BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"QUANTIFICATION OF CRP, DIFFERENTIAL COUNT AND BLOOD SUGAR IN ACUTE CORONARY SYNDROME"** is a bonafide original work of **Dr.P.LENIN** in partialfulfilment of the requirements of M.D General Medicine [Branch-1] examination of The Tamilnadu Dr.M.G.R Medical University to be held in April 2018.

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CERTIFICATE-II

This is to certify that this dissertation work titled **"QUANTIFICATION OF CRP, DIFFERENTIAL COUNT AND BLOOD SUGAR IN ACUTE CORONARY SYNDROME"** of the candidate ,**Dr.P.LENIN** with Registration number **201511552** for the award of **M.D Degree** in the branch of **General Medicine(Branch-1).I** personally verified the urkund.com website for the purpose of plagiarism Check.I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **5(Five)** percentage of plagiarism in the dissertation

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DECLARATION

I solemnly declare that the dissertation titled "**QUANTIFICATION OF CRP, DIFFERENTIAL COUNT AND BLOOD SUGAR IN ACUTE CORONARY SYNDROME**" is done by me at **K.A.P.VISWANATHAM GOVTMEDICAL COLLEGE, TIRUCHIRAPALLI-1** under the guidance and supervision of Prof. **Dr U.B.PADMANABAN M.D**. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of the requirements for the award of M.D Degree [Branch-1] in General Medicine.

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Quantification of CRP, Differential Count, Blood sugar in ACS

INTRODUCTION

Acute Coronary Syndrome (ACS) refers to any condition attributed to obstruction of the coronary arteries which reduces blood flow to the heart, and includes unstable angina and myocardial infarction (MI).The consequences depend on the degree and location of the obstruction and range from unstable angina to non–ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and sudden cardiac death.Symptoms are similar in each of these syndromes (except sudden death) and include chest discomfort with or without dyspnea, nausea, and diaphoresis. Diagnosis is by ECG and the presence or absence of serologic markers[1].The term ACS was adopted because it was believed to more clearly reflect the disease progression associated with myocardial ischemia. Unstable angina and myocardial infarction (MI) both come under the ACS[2].

The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD , whilst the reported prevalence increases with age for both women and men and it has been estimated that approximately every 42 seconds, an American will suffer for an MI. According to the American Heart

Association(AHA), 785,000 Americans will have an MI this year, and nearly 500,000 of them will experience another[3] .

India has the highest burden of ACS in the world. The CREATE registry has provided contemporary data on 20,468 patients from 89 centers from 10 regions and 50 cities in India[2].CAD occurs in Indians 5–10 years earlier than in other populations around the world and the major effect of this peculiar phenomenon is on the productive workforce of the country aged 35–65 years[4].

The prevalence of CAD and the incidence of ACS also are very high among Indians.India has the highest burden of ACS in the world. The rising incidence of ACS in Indians may be related to the changes in the lifestyle, the westernization of the food practices, the increasing prevalence of diabetes mellitus and probably genetic factors[5&6].

Atherosclerosis has been increasingly recognized as a complex and multifactorial inflammatory disease rather being a simply process of lipid accumulation of the wall of the medium sized and large arteries. Inflammation plays a key role in the initiation, progression and complications of atherosclerosis by mediating every stage of the atheroma development. It has been hypothesized that injury of the vascular wall leads to an inflammatory response that involves complex interactions between endothelial and smooth muscle cells, leucocytes and platelets[1]. Several epidemiological and clinical studies reported associations

between the various circulating markers of inflammation, such as C-reactive protein, fibrinogen, adhesion molecules, cytokines, elevated leukocyte count and the different clinical manifestations of coronary heart disease[2].

Elevated leukocyte count, a marker of inflammation, has long been identified as an independent predictor of an increased risk for long term mortality and myocardial infarction both in individuals without cardiovascular disease at baseline and in patients with established coronary artery disease (CAD) [3-8].

Recently, the differential leukocyte count and elevated neutrophil to lymphocyte (N/L) ratio have been the subject of interest in predicting the risk for future cardiovascular events. An elevated N/L ratio has been shown to independently indicate an increased long- term risk of mortality in patients with stable CAD and those with myocardial infarction and offer incremental prognostic value to total leukocyte count [9-11]. How- ever, the relation between the differential leukocyte count, N/L ratio and the presence and severity of CAD has not been extensively studied.In most of the study ,any one of the single parameters like total WBC count with prognosis or C reactive protein with cardiac injury or random blood sugar in acute coronary syndrome has been studied not collectively studied and none of the study,typically assess the cardiac performance in the form of ejection fraction.

The present study is aimed to investigate the amount of sugar in the blood, WBC count,CRP in ACS and to correlate with the severity of the disease.

These parameter can be used to assess the cardiac performance like ejection fraction where there is scarcity of echo machine or non availability of bed side ECHO,patients who are not able to shift to echo room,in that condition & can be utilized in govt taluk hospital ,block phc where echo is not available.

The study of these factors provides a new step in the advancement of the treatment.

AIMS & OBJECTIVES

1. To assess the extent of injury of myocardium by ejection fraction in acute coronary syndrome patients
2. To estimate the level of CRP, differential count, blood sugars in acute coronary syndrome patients.
3. To assess the risk of morbidity & mortality in acute coronary syndrome patients by studying the effects of these parameters of CRP, differential count & blood sugars with ejection fraction.

REVIEW OF LITERATURE

Acute coronary syndromes include

- ❖ Unstable angina
- ❖ Non–ST-segment elevation myocardial infarction (NSTEMI)
- ❖ ST-segment elevation myocardial infarction (STEMI)

These syndromes all involve acute coronary ischemia and are distinguished based on symptoms, ECG findings, and cardiac marker levels. It is helpful to distinguish the syndromes because prognosis and treatment vary[8].

The pathogenetic classification of acute coronary syndrome (ACS) based on simple clinical descriptors provides a basic understanding regarding the mechanisms responsible for coronary instability in homogeneous groups of patients.

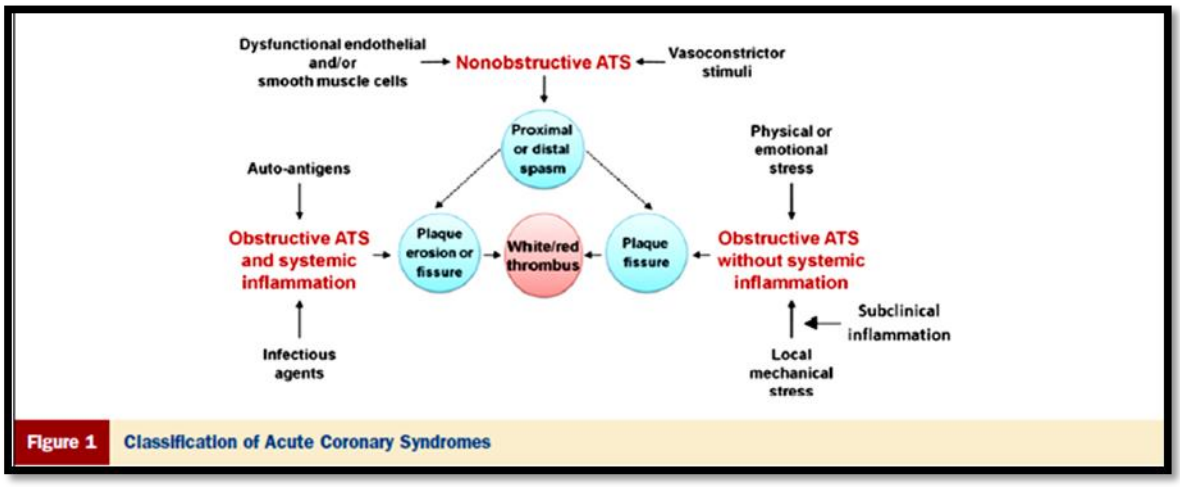


Figure 1 Classification of Acute Coronary Syndromes

1) patients with obstructive atherosclerosis and systemic inflammation
2) patients with obstructive atherosclerosis without systemic inflammation;

3) patients without obstructive atherosclerosis.

This pathogenetic classification of ACS might help in the search of new diagnostic algorithms and therapeutic targets[12].

Etiology

The most common cause of acute coronary syndromes is an acute thrombus in an atherosclerotic coronary artery. Atheromatous plaque sometimes becomes unstable or inflamed, causing it to rupture or split, exposing thrombogenic material, which activates platelets and the coagulation cascade and produces an acute thrombus.

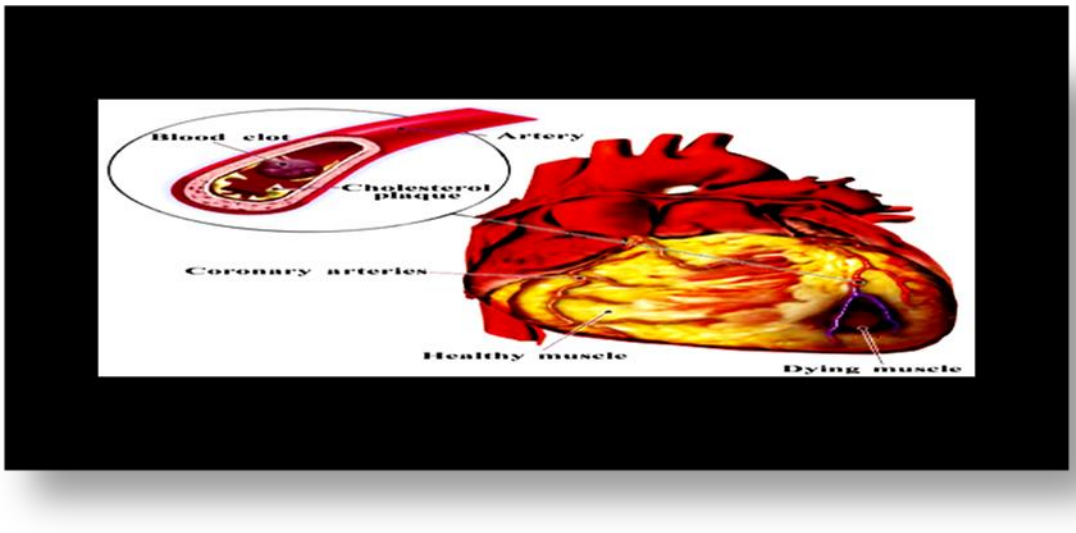
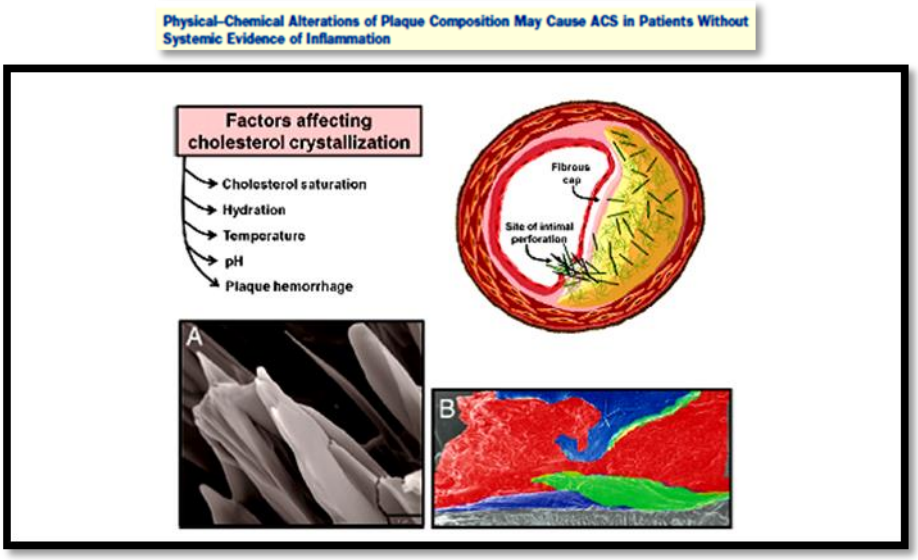


Figure 1. Structure of infarcted heart (Henry Gray, 1918).

Platelet activation involves a conformational change in membrane glycoprotein (GP) IIb/IIIa receptors, allowing cross-linking (and thus aggregation) of platelets. Even atheromas causing minimal obstruction can rupture and result in thrombosis; in > 50% of cases, pre-event stenosis is <40%. Thus, although the severity of stenosis helps predict symptoms, it does not always predict acute thrombotic

events. The resultant thrombus abruptly interferes with blood flow to parts of the myocardium. Spontaneous thrombolysis occurs in about two thirds of patients; 24hr later, thrombotic obstruction is found in only about 30%. However, in virtually all cases, obstruction lasts long enough to cause tissue necrosis.



Effects of cholesterol crystals on plaque integrity in coronary arteries of patients who died of acute coronary syndrome (ACS) assessed by using light and scanning electron Microscopy.

- A and B show scanning electron microscopy results of the culprit stenosis from the left anterior descending artery of a 57-year-old woman who died of ACS.
- (A)Example of cholesterol crystals perforating the intimal surface at the plaque shoulder (bar _ 10 _m).

- (B) A color-coded image defines thrombus (red), fissured plaque (blue), and the site of a cholesterol crystal perforating the intima (green-yellow). (Abela et al)[13].

Risk factors:

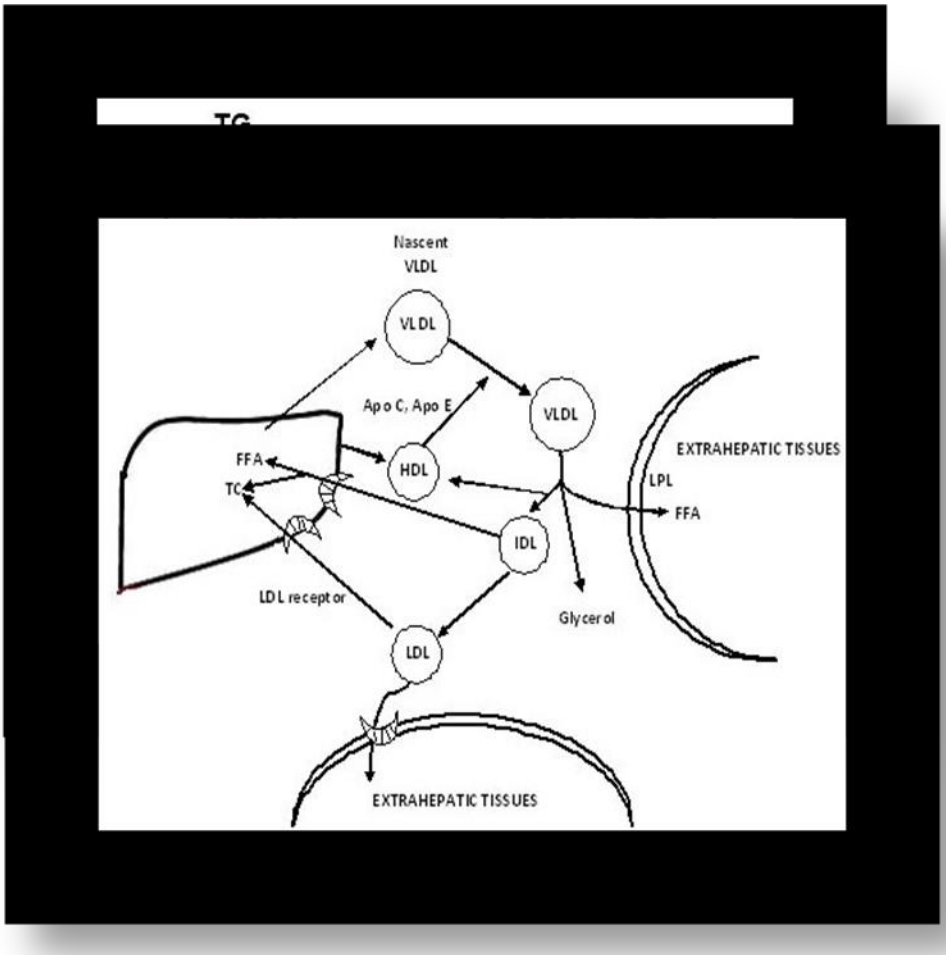
The high death rate of myocardial infarction are due to high levels of standard risk factors and a low level of intervention those risk factors.

- Population based studies have given rise to the concept that specific factors such as genetic, environmental, modifiable and non-modifiable factors are primarily responsible for the increased risk of myocardial infarction[14]
- The Major modifiable risk factors are hypercholesterolemia, diabetes milletus, hypertension and cigarette smoking.
- Other modifiable risk factors include lowered high-density lipoprotein (HDL) cholesterol level, excessive alcohol use, obesity ,unhealthy diets, and physical inactivity etc.
- Several independent risk factors for CVD include non-modifiable (family history, male sex, and advancing age) and modifiable risk factors.

LIPID METABOLISM:

Dietary fat (triglyceride) is hydrolyzed to free fatty acids and glycerol (actually monoacylglycerol) in the intestine by pancreatic lipase. Short chain fatty acids can enter the circulation directly, but most fatty acids are reesterified with glycerol in the epithelial cells of the intestine.

Fig-a and b shows the overview mechanism of lipid metabolism (Murray et al., 2000)



The resulting triglycerides enter the circulation as lipoprotein particles called chylomicrons through the lymphatic system. The triglycerides in chylomicrons can be cleared by lipoprotein lipase at the endothelial surface of capillaries. The resulting fatty acids can be stored as fat in adipose tissue, used for energy in any tissue with mitochondria and an ample supply of O_2 and reesterified to triglycerides in the liver and exported as lipoproteins called VLDL (Murray *et al.*, 2000) changes[15].

The initial particle produced by the liver is very low density lipoprotein (VLDL). This particle is large and rich in triglycerides. It undergoes degradation within the circulation by lipoprotein lipase with the metabolism of triglycerides. The particle then becomes smaller in size and more dense and cholesterol laden, eventually forming low-density lipoprotein (LDL), which is the primary atherogenic particle. LDL, particularly oxidized LDL, can be taken up by macrophages in the arterial wall and both incite and contribute to the atherosclerotic lesions. Circulating LDL particles can undergo reuptake in the liver via specific receptors and get cleared from the circulation. Approximately 30% of LDL is degraded in extrahepatic tissues and 70% in the liver.

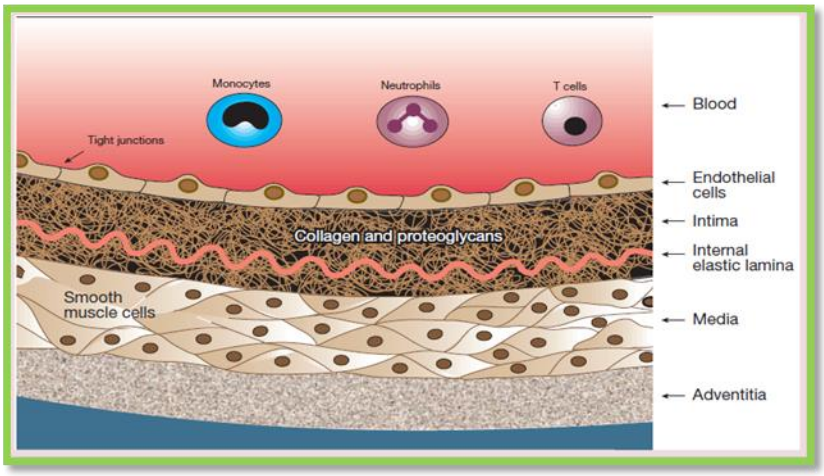
An additional circulating particle, which is small and cholesterol – rich is called high density lipoprotein (HDL). HDL participate in reverse cholesterol transport (Cholesterol removal from deposits in the arterial wall) and to have antioxidative properties. The majority of cholesterol is endogenously synthesized.

HMG-CoA reductase is a rate limiting enzyme in the endogenous cholesterol synthetic pathway, blockade of which provides an important opportunity for pharmacological therapy. Endogenously synthesized cholesterol and triglycerides are packaged by the liver into soluble particles consisting cholesterol ester and triglyceride rich core surrounded by phospholipid membrane that carries various apolipoproteins. The apolipoproteins have many properties, including the provision of recognition sites for various receptors, which lead to specific metabolism of these particles within the circulation [16 , 17]

Events in atherosclerosis:

Normal Artery

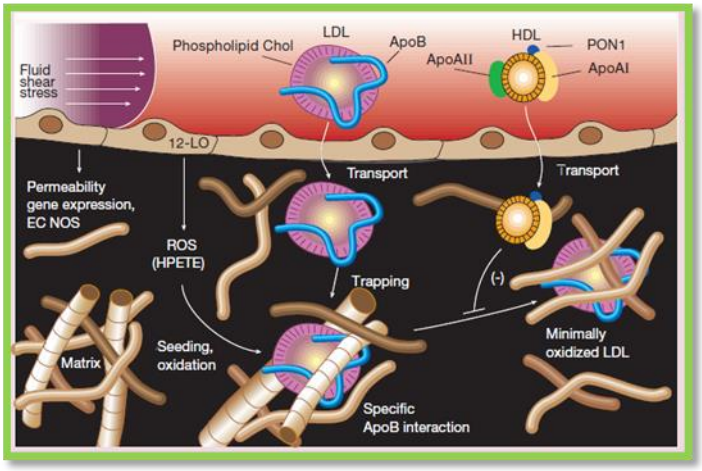
The development of atherosclerosis is a complex process. Substances such as fats, cholesterol, fibrin, platelets, cellular debris and calcium are deposited in the artery wall. Gradually these substances build up and eventually narrow and block the artery similar to scale forming on the insides of pipes (Libby, 1999) [18].



Normal artery

1. Lesion initiation

High plasma LDL accumulated in the subendothelial matrix is a primary initiating event in atherosclerosis. LDL diffuses passively through endothelial cell junction and its retention in the vessel wall seems to involve interactions between the LDL constituent apoB and matrix proteoglycans (Boren *et al.*, 1998). LDL does indeed



Lesion initiation

undergo modification including oxidation, lipolysis, proteolysis and aggregation. Such modifications contribute to inflammation as well as foam cell formation. Most significant modifications for early lesion formation are lipid oxidation as a result exposure to the oxidative waste of vascular cells. Oxidation of LDL is inhibited by HDL, which contains the antioxidant protein 'paraoxonase' (Hegele, 1999).

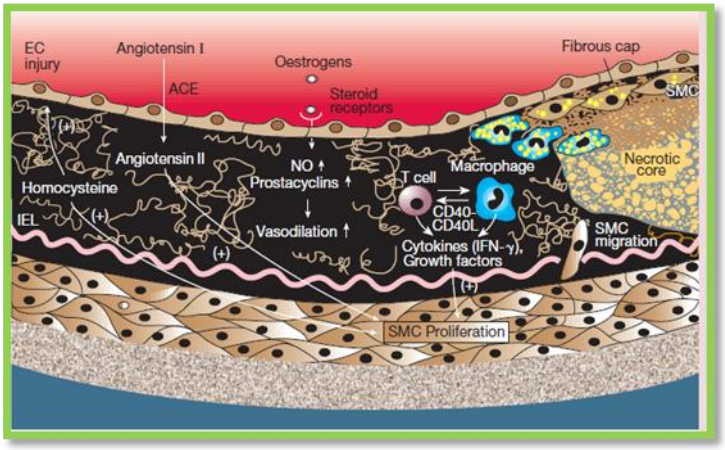
2.Inflammation

Accumulated minimally oxidized LDL stimulates the overlying endothelial cells to produce adhesion molecules such as monocyte chemotactic protein-1

(MCP-1) and growth factors such as macrophage colony-stimulating factors (M-CSF), resulting in the recruitment of monocytes to the vessel wall. Oxidized LDL also inhibits the production of nitric oxide (NO), an important mediator with anti-atherogenic properties, including vaso relaxation. The entry of particular leukocytes into the artery wall is mediated by adhesion molecules and chemotactic factors. Among the endothelial cell adhesion molecules likely to be important in the recruitment of leukocytes are ICAM-1, P-selectin, E-selectin, PCAM-1 and VCAM-1. Adhesion molecules on monocytes include β_2 - integrin, integrin VLA-4 and PCAM-1. Advanced glycation end products (AGE_S) are formed in diabetes and these promote inflammation via specific receptors on endothelial cells .

3.Foam Cell Formation

LDL must be extensively modified (highly oxidized) before it can be taken up rapidly by macrophages to form foam cells. Highly oxidized aggregated LDL is formed in the vessel as a result of the action of reactive oxygen species (ROS) and the enzyme sphingomyelinase (SMase), secretary phospholipase-2 ($sPLA_2$), other lipases and myeloperoxidase (MPO). The oxidized aggregated LDL is recognized by macrophage receptors such as SR-A, CD36 and CD68 (Leitinger *et al.,* 1999; Podrez *et al.*, 2000). Scavenger receptor expression is mediated by cytokines such as tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ).

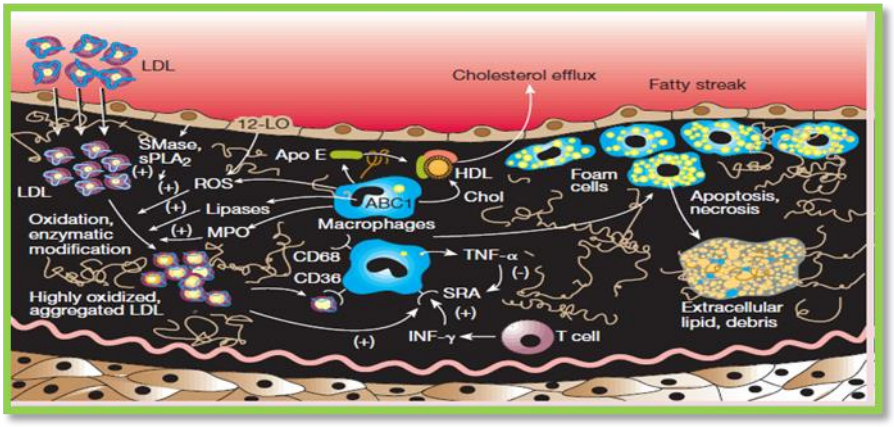


Foam cell formation

Foam cells secrete apolipoprotein E, which may facilitate removal of excess cellular cholesterol. The death of foam cells leaves behind a growing mass of extracellular lipids and other cell debris (Suzuki *et al.*, 1997).

4. Formation of fibrous plaques:

Fibrous plaques are characterized by a growing mass of extracellular lipid mostly cholesterol and its ester and by the accumulation of smooth muscle cells (SMCs) and SMC-derived extracellular matrix. A number of risk factors, including elevated levels of homocysteine and angiotensin II stimulate the migration (or) proliferation of SMCs.



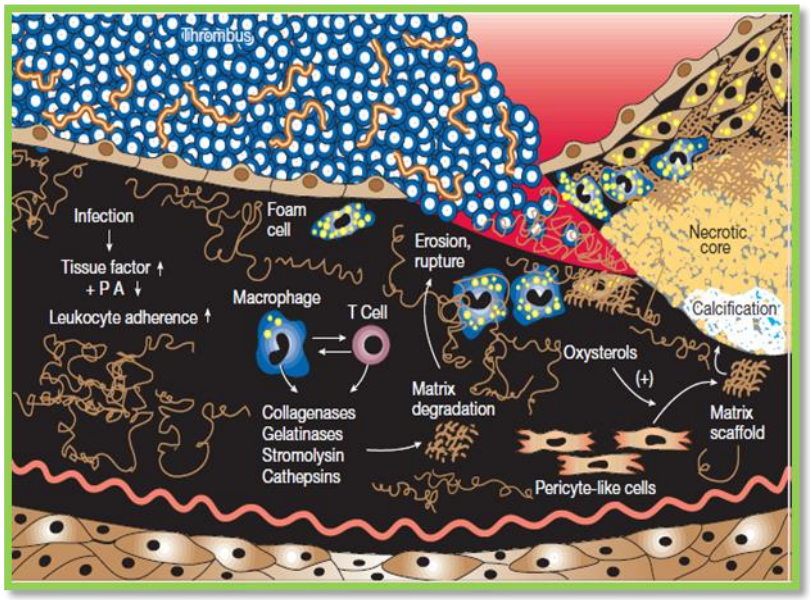
Formation of fibrous plaques

Oestrogens exert beneficial effects on plasma lipoprotein levels and they also stimulate the production of NO and prostocyclin by endothelial cells. The interaction of CD40 and CD40 ligand stimulates T lymphocytes and macrophages to express cytokines such as IFN-γ that can influence inflammation, SMC growth and matrix accumulation. The intimal SMC secrete extracellular matrix and give rise to a fibrous cap (Schonbeck *et al.*, 2000).

5. Complex lesions and thrombosis:

Vulnerable plaques with in fibrous cap result from degradation of matrix by various proteinases such as collagenases, gelatinases, stromolysin and cathepsins and by inhibiting matrix secretion. Among various factors that may destabilize plaques and promote thrombosis are infection which may have systemic effects such as induction of acute phase proteins and local effects such as increased expression of tissue factor and decreased expression of plasminogen activator

(PA). Intimal calcification is an active process in which pericyte like cells secrete a matrix scaffold which subsequently becomes calcified, akin to bone formation.



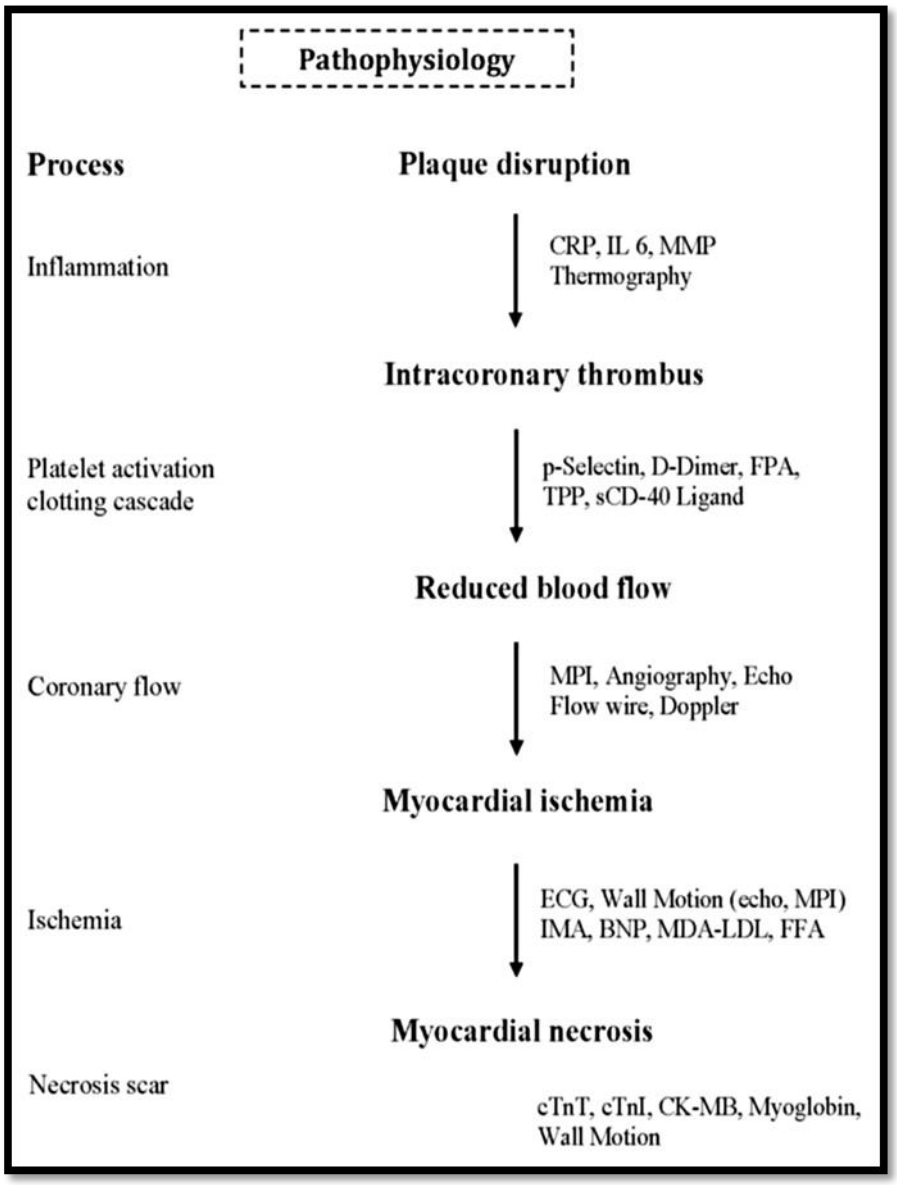
Complex lesions and thrombosis

Thrombus formation consisting of adherent platelets and fibrin cross links, usually results from plaque rupture, exposing tissue factors in the necrotic core (Watson *et al.*, 1994; Libby, 1999)

PATHOPHYSIOLOGY OF ACS:

ACS begins when a disrupted atherosclerotic plaque in a coronary artery stimulates platelet aggregation and thrombus formation. It's the thrombus occluding the vessel that prevents myocardial perfusion.

FigureMechanism of action and targets for detection of acute coronary syndromes (ACSs) [Pandey Shivanand, 2010



In the past, researchers supposed that the narrowing of the coronary artery in response to thickening plaque was primarily responsible for the decreased blood flow that leads to ischemia, but more recent data suggest that it's the rupture of an unstable, vulnerable plaque with its associated inflammatory.

MYOCARDIAL ISCHEMIA:

Ischemia can also be described as an inadequate flow of blood to a part of the body, caused by constriction or blockage of the blood vessels supplying it. Ischemia of heart muscle produces angina pectoris. Since oxygen is mainly bound to hemoglobin in red blood cells, insufficient blood supply causes tissue to become hypoxic, or, if no oxygen is supplied at all, anoxic. In aerobic tissues such as heart and brain, necrosis due to ischemia usually takes about 3-4 hours before becoming irreversible. However, complete cessation of oxygenation of such organs for more than 20 minutes typically results in irreversible damage. In many cases, obstruction of the coronary artery by thrombus is minimal, resulting in little or no impairment to coronary flow. Alternatively, the thrombus can result in total occlusion of the artery with classic symptoms and ECG findings. The combination of reduced blood flow and increased oxygen demand precipitates the critical imbalance of oxygen supply and demand that leads to myocardial ischemia (i.e., unstable angina). Persistent ischemia can result in myocyte death, which may be detected using biomarkers of necrosis and forms the basis for the diagnosis of AMI[14].

Rarer causes of acute coronary syndromes:

1. **Coronary artery embolism** can occur in mitral or aortic stenosis, infective endocarditis, or marantic endocarditis.

2. **Coronary spasm**-induced MI may occur in normal or atherosclerotic coronary arteries[9].

Diagnosis:

A diagnosis of ACS should be considered in all patients presenting with ischemic symptoms. Clinical signs and symptoms of ischemia include

- various combinations of chest pain,which radiates to the left arm, right shoulder, or both arms is more likely to be associated with MI
- upper extremity, mandibular or epigastric discomfort. The pain and discomfort associated with an ACS event may occur with exertion or at rest and is often diffuse rather than localized
- dyspnea,
- diaphoresis,
- nausea,
- fatigue or syncope.

In certain situations, ACS may be associated with palpitations, cardiac arrest, or with an asymptomatic clinical presentation[10]

Differential Diagnosis:

It is important to remember that MI represents myocardial necrosis due to myocardial ischemia.

- clinical conditions such as pericarditis, dissecting aortic aneurysm, and mitral valve prolapse represent non ischemic cardiac causes of myocardial injury and thus do not fall within the definition of ACS.
- several noncardiac conditions that may manifest with similar symptoms of ACS, including musculoskeletal pain, esophageal discomfort, pulmonary embolism, or anxiety.

It is essential to determine the correct etiology of a patient's signs and symptoms to determine an appropriate management plan.

Cardiac Biomarkers:

Cardiac troponins are biochemical markers of myocardial damage[1], which has high clinical sensitivity and myocardial tissue specificity. An elevation in troponin concentration is based on specific assays and is defined as a value exceeding the 99th percentile of a normal reference population. At this level, sensitive cardiac troponin I assays have a positive likelihood ratio (LR) of 11–14 and a negative LR of 0.06–0.15[6]. Troponin levels should be measured on first assessment, within 6 hours of the onset of pain, and in the 6–12 hour time frame after onset of pain, due to the delayed increase in circulating levels of cardiac biomarkers .In addition, it is important to understand that elevations in troponin may be seen for upto 2 weeks after the onset of myocardial necrosis. It is essential to detect a rise and/or fall in cardiac biomarkers to distinguish acute from chronic

elevations in troponin concentrations, which may be associated with structural heart disease.

If troponin concentrations are unavailable, then CKMB should be measured[1].Ideally, both troponin and CKMB should be obtained during evaluation for ACS due to the different concentrations of these biomarkers over time and the added diagnostic value of serial testing (strength of recommendation A) [2,3].For example, serial measurement of CKMB has a positive LR of 20 and negative LR of 0.22[8].

Increases in cardiac biomarkers, notably cardiac troponin (I or T), or the MB fraction of creatine kinase (CKMB), signify myocardial injury leading to necrosis of myocardial cells.But the elevated cardiac biomarkers do not indicate the underlying mechanism of injury and do not differentiate between ischemic or non-ischemic causes[1].There are several clinical conditions that have the potential to result in myocardial injury and cause elevations in cardiac biomarkers, including acute pulmonary embolism, heart failure (HF), end-stage renal disease, and myocarditis[7]. As a result, cardiac biomarker elevations cannot be utilized in isolation to make a diagnosis of MI[1].

C-Reactive Protein in ACS:

CRP belongs to the pentraxin protein family and is synthesized in hepatocytes and some extrahepatic tissues, such as vascular smooth muscle,

atherosclerotic plaques, intracardial tissues[65]. There are two CRP types with different qualities: pCRP (pentamer) and mCRP (mono-mer). mCRP evolves when the pentamer is dissociated and is synthesized by the cells which are activated by the pathologi-cal process (tissue necrosis, trauma, infection and related mediators: interleukins IL-1, IL-2, IL-17 and tumor necrosis factor alpha [TNFa]). mCRP has proinflammatory and pro-thrombotic qualities[66] ·Inflammation is considered to be an essential factor in atherosclerosis and acute coronary syndromes (ACS) development by stimulating atheroma formation, destabilization of damaged atherosclerotic plaques and formation of occlusive thrombi[3]In case of chronic low-intensity inflammation CRP damages the glycocalyx of vascular endothelium, causing its dysfunction[67.]

Moreover, the processes of endothelium-dependent vasodilatation, endothelial stem cell migration and adhesion are disturbed and apoptosis is induced. Infiltration of vascular wall with inflammatory cells, neutral lipid deposition in arterial intima is stimulated and macrophages use up plasma low-density lipoproteins (LDL) easier, forming foam cells. Vascular smooth muscle cells proliferate faster, migrate to the intima and synthesize more extracellular matrix. Inflammatory cells boost up metabolic activity in vascular walls making the medium more acidic, which in turn promotes faster smooth muscle cell apoptosis. By activating the angiotensin-aldosterone system, angiotensin-1 and angiotensin-2 receptors, CRP promotes proatherogenic activity of angiotensin,

directly and indirectly stimulates structural and functional modification of arterial walls, heart and vascular remodeling, vascular stiffening, increment of peripheral vascular resistance, interferes with arterial blood pressure (ABP) regulation mechanisms [67].

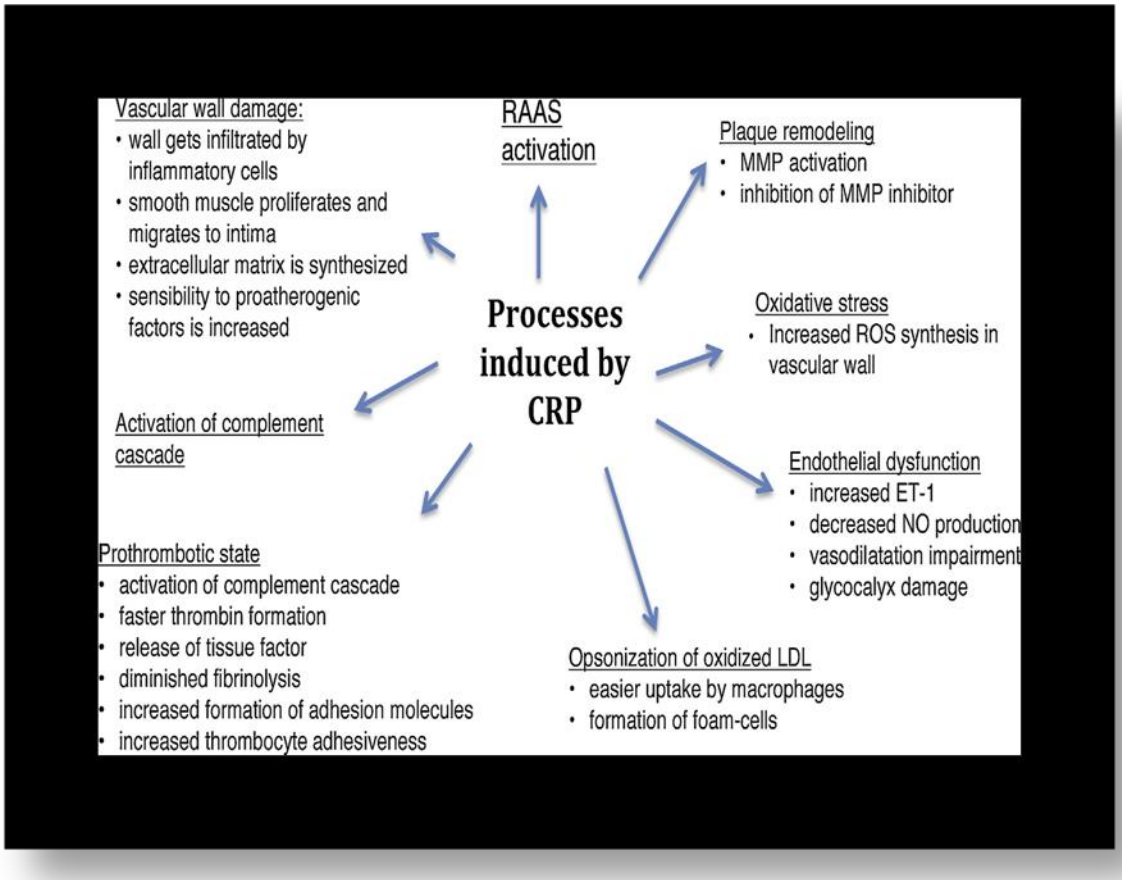


Figure – C-reactive protein pathogenesis. CRP, C-reactive protein; ET-1, endothelin-1; NO, nitric oxide; MMP, matrix metalloproteinase, ROS, reactive oxygen species; RAAS, renin–angiotensin–aldosterone system.

C-Reactive Protein is an acute phase inflammatory mediator in cardio vascular disases[22].CRP is a protein ,which is part of the innate immunity that attracts the classical complement pathway after aggregation or binding to ligands .CRP also binds to phospholipids of damaged cells & enhance uptake of these cells by macrophages.CRP posses proatherogenic properties.It activates macrophages to express cytokines properties & enhance the uptake of LDL.

So high sensitive CRP is an easily measured & widely investigated biomarker of inflammation.Hs- CRP is a chemotactic factor inside fibrinogen & it makes the macrophages to adhere to the endothelial surface, which cause migration into the intima, thus promoting plaque rupture and vasoconstriction.In addition to this it promote monocytes to release tissue factor which initiate the extrinsic coagulation system and promote thrombosis(beaudeux et al 2004)[23].

The guidelines of ESC 2012 recommend that hsCRP may be tested in patients with moderate CVD risk (II B) and not recommended to be tested for low risk asymptomatic or high risk patients (III). Drawbacks of this test are also mentioned:

(1) effects of confounding variables,

(2) narrow diagnostic window regarding hsCRP concentration and CVD risk,

(3) lack of causality relationship between hsCRP and CVD risk,

(4) shortage of specific treatment that would decrease CVD incidence by decreasing hsCRP concentration[19] .

Among these several inflammatory biomarkers tested in ACS, levels of C-reactive protein (CRP) assessed by using high-sensitivity CRP (hs-CRP) assays represent an obvious candidate because CRP is a prototypic marker of inflammation characterized by high sensitivity and a wide dynamic range . However, it is difficult to establish a cut off for hs -CRP. In primary prevention, hs-CRP levels _2 mg/l (and even _1 mg/l) might be helpful in guiding therapy ; but in patients with ACS, 2 different cutoffs have been suggested as clinically useful on the basis of our initial observations: an admission value _10mg/l and a discharge value _3 mg/l. These cutoffs, although confirmed in larger studies , have not yet obtain general consensus

Role of WBC in ACS:

The WBC count might serve as a marker for one or more disease processes that lead to vascular injury and ultimately to ischemia.

Pressure-dependent plugging of microvessels by Leukocytes:

The diameters of erythrocytes and leukocytes are greaterthan the internal diameters of most nutritive capillaries, the rheologic properties of blood cells are major determinants ofmicrovascular perfusion. WBCs exert an influence on blood flow disproportionate to their number for two reasons:

- First, leucocytes are larger than red blood cells and spherical in shape.
- Second, they are much stiffer than red blood cells, with an average cytoplasmic viscosity 1000-fold that of red blood cells [13–15]. Thus, the

capillary transit of WBCsis frequently associated with slowing, or even momentary stoppage, of blood flow [20]

Rheological abnormalities of leukocytes:

- Since normal WBCs face difficulties in traversing capillaries, it follows that alterations in the rheologic properties of the leukocytes might have a major impacton microvascular flow and thus might provide anotherpathophysiologic link between these cells and tissue ischemia.

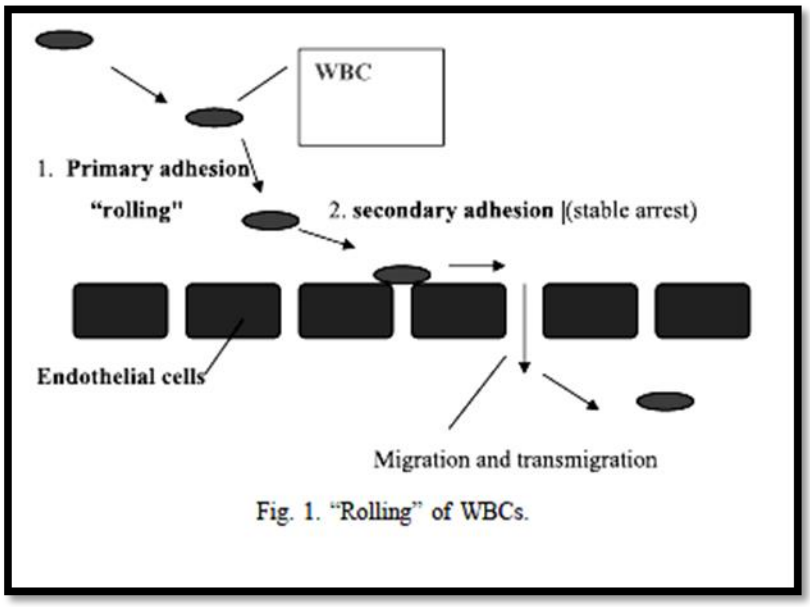


Fig. 1. "Rolling" of WBCs.

- Another factor is the increased leukocyte adhesiveness, which may be provoked by a variety of stimuli.Craddock et al. found that granulocytes shared withplatelets the ability to aggregate when stimulated andthus—at least theoretically—to embolize to microvascularites . Such aggregation has been shown to occur in vitro in response not only to complement activation(with the activation of C5a), but also to bacterial oligopeptide

chemotaxins ,immune complexes and certain complex lipids such as leukotriene B4 [21]

Endothelial cell injury caused by leukocytes:

Once the granulocyte has arrived at a microvascular site inan activated state—either by embolization in an aggregateor by an increase in its tendency to adhere to endothelial cells—it can deliver a variety of insults to the vessel lining[21]

. **Cell adhesion molecules' effects:**

It has been demonstrated that there was an increase in procoagulant activity in patients who underwent successful primary angioplasty for AMI and that this increase in procoagulant activity was associated with an increase in Mac-1 expression on circulating leukocytes. Finally, the adherence of activated platelets to polymorphonuclear leukocytes via Mac-1 mayalso play a role in thrombus formation[22.] Myocardial ischemia/reperfusion induces ventricular reperfusion arrhythmias. It is known that activated leukocytes release oxygen free radicals, and that intercellular adhesion molecule-1 (ICAM-1) plays a major role in leukocyte activation and infiltration. A prospective study compared two groups of AMI patients, all of them underwent percutaneous balloon angioplasty (with or without reperfusion arrhythmias). The plasma soluble ICAM1 levels at admission were significantly greater in patientswith reperfusion arrhythmias ($P<0.05$). Plasma soluble ICAM-1 levels were followed for 3 weeks, and it was found that ICAM-1 levels were consistently higher in the group of patients with reperfusion arrhythmias. Simple regression analysis showed no significant relationship

between plasma ICAM-1 levels and age, systolic and diastolic blood pressures, or serum creatine kinase activity.The increase in the plasma levels of ICAM-1 was observed in patients manifesting ventricular reperfusion arrhythmias. This increase in ICAM-1 levels was observed as early as at admission. The increased plasmaI CAM-1 levels may be a useful biochemical markerfor predicting myocardial reperfusion injury such as reperfusion arrhythmias in AMI[23].

Cytokine's effects:

The inductionof monocyte procoagulant activity with either IL-6 or IL-8has been proposed as a possible link between the inflammation and thrombosis in patients with coronary artery disease.Neuman et al investigated the effects of both of these cytokines on monocyte tissue factor (TF) expression, because the assembly of TF with factor VIIa initiates the extrinsic pathway of the coagulation cascade [24] . Furthermore, this increase in procoagulantactivity was induced at concentrations found in peripheral blood of patients with AMI .

The role of T-lymphocytes:

It has been noted that low CD4/CD8 ratio andlow CD4 cell count on the first day of AMI were strongly correlated with low left ventricular ejection fraction and high myocardial mass destruction as reflected by CPK levels. Patients with the lowest CD4 count on admission and those whose CD4 counts did not rise had reinfarctionor death. Significantly higher levels of sIL-2R andIL-1_ were found in the AMI patients compared with the healthy control group. Patients who suffered reinfarction had increased cytokine levels toward the seventh day; the

higher the level, the lower the left ventricular ejection fraction and the greater the probability of death[25]

The peripheral leucocycte count provides an assessment of the inflammatory status[65.]The leucocyte response which is triggered by the necrotic insult in MI is considered as expression of acute –phase reactant[66]. Circulating leucocyte-platelet aggregates appars in ACS which facilitate vascular plugging & infarct extension[67].

Atherosclerotic plaque is characyterisd by infiltrates of monocyte /macrophages & lyphocyctes which is transmigrated from the vasculsar space into the subendothelial layers of large & medium sized vessels[26].The linkage of monocyte & T lymphocytes causes activation of one cells which in turn leads to activation of other type of cells. This activated T lymphocyctes secretes certain inflammatory cytokines such as gama macrophages vascular endothelial cells & smooth muscle cells.The null T cells which are present in increased number in peripheral blood of ACS patient are capable to injure the vessel directly.the neutrophil appears early in the infarct zone with heavy infiltrate by 1-3 days,followed by infarct healing & replacement fibrosis[66]. The neutrophils make disruption by releasing proteolytic enzymes,derivatives of arachidonic acid & superoxide radicles[29].Neutropils ,monocytes and special tissue macrophages (in atherosclerotic plaque) secrete myoperoxidase,an enzyme formed by the activation and degranulation of leucocytes.These myoperoxidase increase foam

cell production and decreased nitric oxide level.the higher level of myoperoxidase in leucocytes is an important prognostic factor in cardiac patient[32].

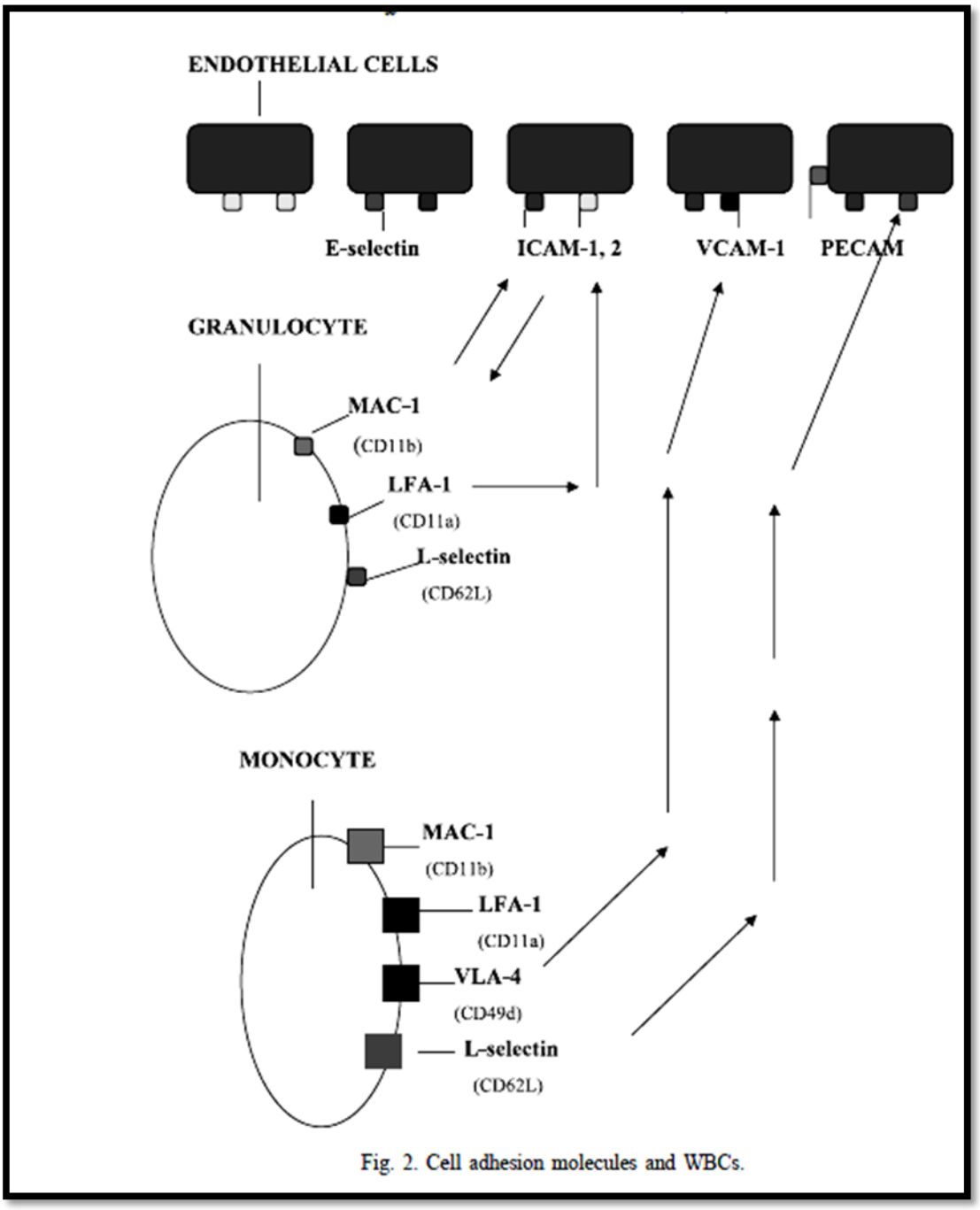
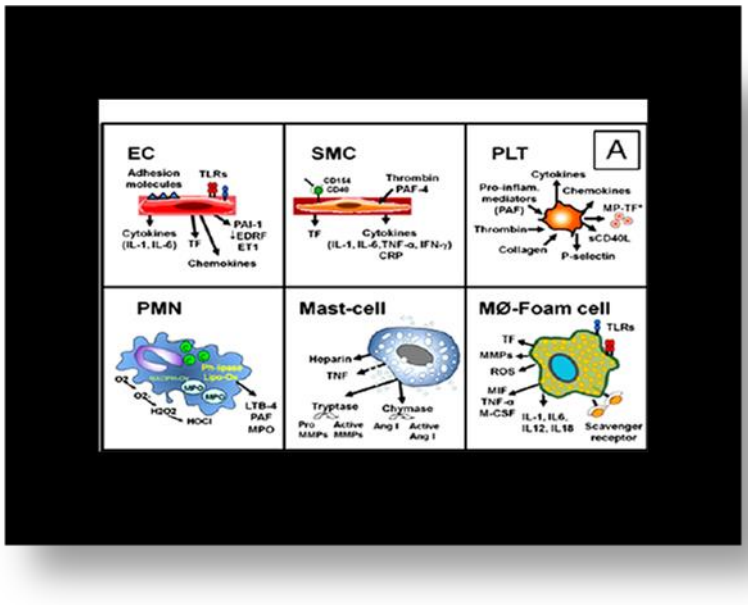


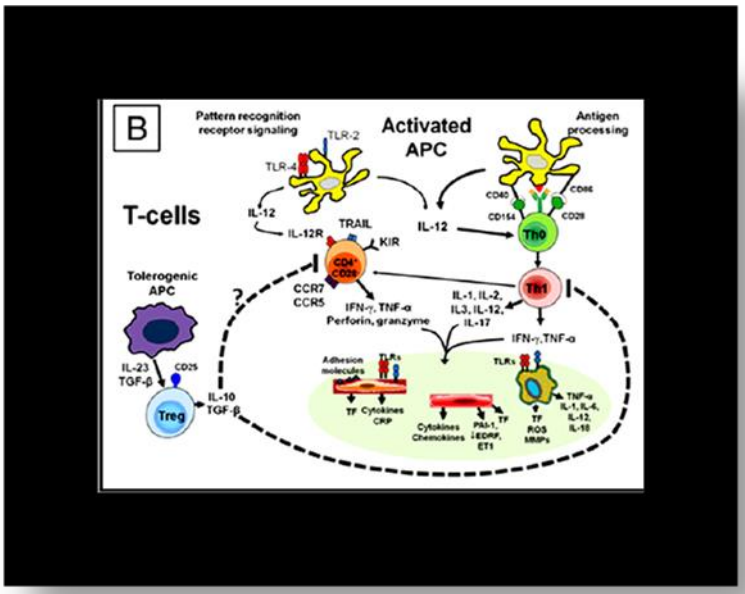
Fig. 2. Cell adhesion molecules and WBCs.

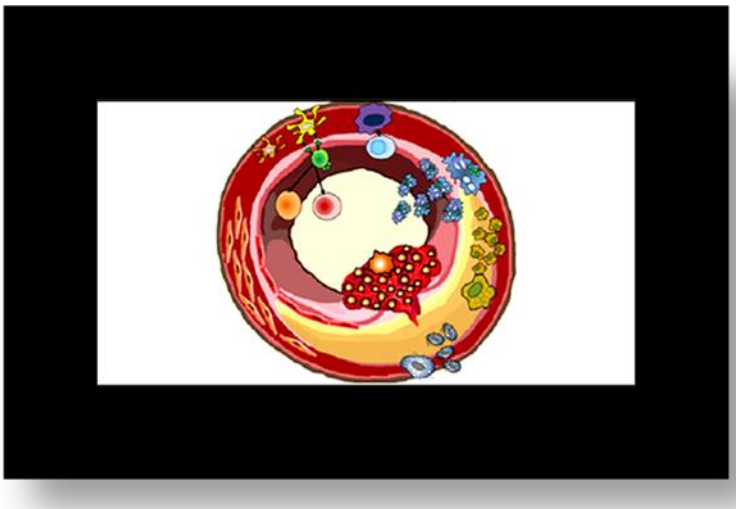
The 3 main features of inflammation associated with ACS are:

1) widespread involvement of epicardial arteries, coronary microcirculation, and even myocardium;
2) activation of innate immunity;
3) **activation of adaptive immunity.**



(A) .Innate immunity





(B) adaptive immunity

Both (A) innate immunity and (B) adaptive immunity play a key role in the pathogenesis of coronary plaque instability.

- (A)All types of inflammatory cells are present in atherosclerotic plaques. Macrophages and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where the atheroma grows and where the risk of plaque rupture is higher.
- (B) T-cell infiltrates are always present in atherosclerotic lesions, and their activation may play a primary role in the transition from stable to unstable plaques.Such infiltrates are predominantly CD4_ T cells, which recognize protein antigens (such as oxidized low-density lipoprotein, human heat shock protein 60, and chlamydial proteins) processed and presented by activated antigen-presenting cells (APCs). Recently, attention has been focused on the possible role of type 17 helper T cells (Th17), known to play critical roles in the development of autoimmunity and allergic reactions by producing interleukin (IL)-17 and, to a lesser extent, tumor necrosis factor (TNF)-beta and IL-6.
- Another subset of Th1 cells in the plaque has the CD4_CD28null phenotype. These T cells have important plaque-destabilizing properties. Regulatory T cells (Treg) maintain the homeostasis of cell subsets involved in adaptive immunity. In human atherosclerotic lesions, Treg colocalize with IL-10 and transforming growth factor (TGF)-_1 expression. .

Hyperglycemic status in ACS syndrome:

Hyperglycemia is an accelerating factor for the evolution of CAD. There are three main hypotheses as to why hyperglycemiaportends higher mortality in acutely ill patients(overview shown in Fig. 1).

- First, elevated blood glucose can be a physiologic response to hormones, such as epinephrine or cortisol, that are released under high systemic stress and, hence, may indicate greater overall illness severity[28]
- Second, hyperglycemia may be an indicator of systemic and organ-specific metabolic dysregulation, especially impaired insulin signaling.In this regard, insulin resistance causes not only hyper glycemia but also may lead to a reduction in energy production in the heart and other organs, producing a lower tolerance to hypo perfusion. In a similar vein, reduced insulin signaling may increase vulnerability to ischemic injury because downstream molecules in the insulin signaling cascade have well-established cytoprotective effects and these are lost when insulin-signaling pathways are disrupted.
- Third, acute hyperglycemia is implicated in the activation of other pathologic processesthat could contribute to cellular and tissue injury, such as increasing free radial formation antioxidative stress, inducing of a prothrombotic state and worsening endothelial function .

The hyperglycemia in serum is correlated with the increased levels of miR-223, miR-92a, miR-486 in sera and HDL, these miRNAs associated with HDL being able to discriminate between ACS and SA patients. Exposure of human macrophages to ACS sera compared to SA sera determines an increase of the production of miR-223, miR-92a, miR-486, miR-125a and miR-146a by the upregulation of Drosha, DGCR8 and Dicer expression, this effect being augmented by the increase of sera's glucose concentration[33].Cardiovascular stress induce release of catecholamines, cortisol, glucagons leading to increase in glucose and free fatty acids that enance hepatic gluconeogenesis & diminished peripheral glucose uptake. Unfavourable effects of high blood glucose levels in myocardial infraction involve impaired left ventricular function,increased incidence of the no-reflow penonmenon, and a tendency for arrhythmias. Hyperglycemia in acute myocardial ischemia leads to several mechanism of enhanced oxidative stress, the activation of blood coagulation and platelets,stimulation of inflammation, and endothelial cell dysfunction[29].

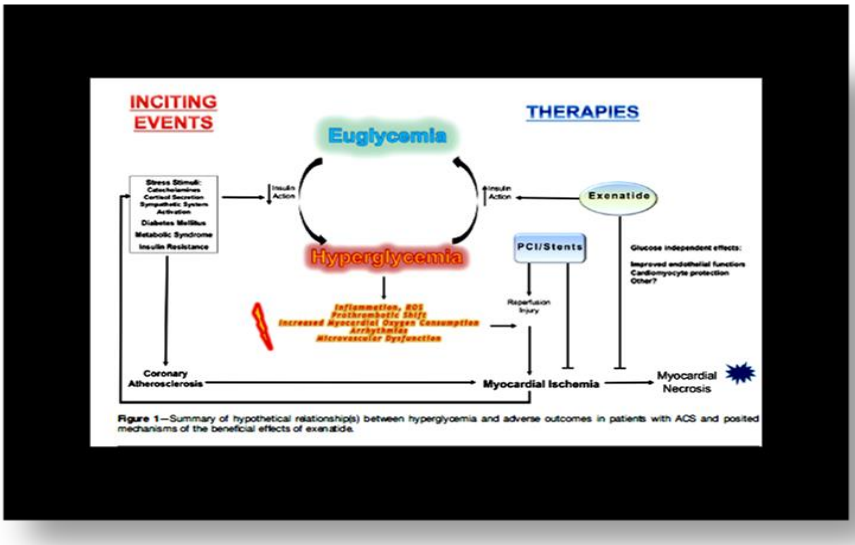


Figure 1—Summary of hypothetical relationship(s) between hyperglycemia and adverse outcomes in patients with ACS and posited mechanisms of the beneficial effects of exenatide.

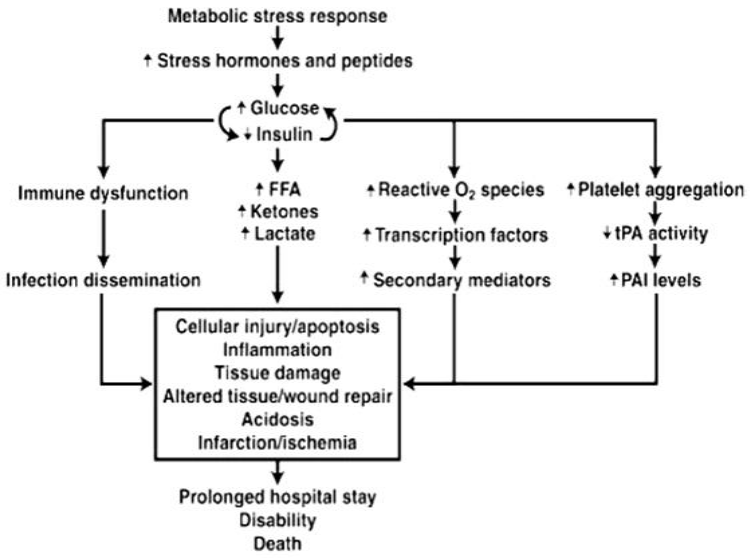


Figure 3. Detrimental physiological impact of hyperglycemia. Modified from Clement et al.[57] FFA indicates free fatty acids; tPA, tissue plasminogen activator; and PAI, plasminogen activator inhibitor.

ECG Changes:

ECG abnormalities that are potentially reflective of myocardial ischemia include changes in the PR segment, the QRS complex, and the ST-segment. The evaluation of ECG changes can assist in estimating time of the event, amount of myocardium at risk, patient prognosis, and appropriate therapeutic strategies. ST-segment elevation found on an ECG is the hallmark sign of a STEMI [1].

Similar to cardiac biomarkers, the ECG alone is often insufficient to make the diagnosis of an acute MI, and the sensitivity and specificity of ECG are increased by serial assessments[9].ECG changes such as ST deviation may also be present in other conditions, such as left ventricular hypertrophy, left bundle branch block, or acute pericarditis[1].

Initial ACS Management is essential to evaluate patients with suspected ACS immediately to prevent potentially fatal clinical consequences and relieve ongoing ischemia.

Early risk stratification should be performed that is inclusive of a patient's demographics and medical history, physical examination, ECG, and cardiac biomarker measurements (strength of recommendation A. Early risk stratification can assist in determining whether a patient should be managed with either an early invasive strategy or an initial conservative strategy and can help determine the pharmacologic therapies that are recommended.

Treatment :

- Oxygen to maintain SaO2 level at > 90% Nitroglycerin or morphine to control pain
- β-blockers, angiotensin-converting enzyme inhibitors, statins (started on admission and continued long term), clopidogrel (Plavix), unfractionated heparin or low- molecular weight heparin, and glycoprotein IIb/IIIa inhibitors [20,21]

DRUG THERAPY : Initial drug therapy for patients presenting with angina includes aspirin, oxygen, nitroglycerin, and morphine sulfate[2]:

HISTORICAL REVIEW:

Christophare et al in 1993 conducted a study in 443 patients with diabetes and 923 patients without diabetes .They compared these groups of patients and they concluded that patients with diabetes are at higher risk when compared with patients without risk[23].

In 1996 ,Steven M. Green et al done a retrospective cross sectional study in 39000 yearly ED visit .The intial WBC count was significantely higher for the subjects who had the AMI.Logistic regression analysis confirmed that leucocytosis is an independent predictor of AMI.They concluded that leucocytosis is significantly associated with MI and this is a weak but independent laboratory predictor.The combination of the WBC and CK-MB may have additional

diagnostic value over an isolated CK-MB result.They explained that prognostic assessment of the role of the WBC count in clinical discussion making should address its complimentary role to that of other clinical and ancillary test parameter[31].

Another study conducted by klar Malmberg etal in 1999,this report describes that the long term outcome in diabetic patients with myocardial infarction is predicted by age ,previous myocardial damage and not the least the actual glucometabolic state[32].

Aldelade etal in 2009 done a retrospective observational cohort study in MI patient in a geographically defined population Olmsted country. From his study he concluded that absolute Neutrophil count was strongly and independently associated with death and heart failure in post MI patient and also concluded that it provides an incremental value in risk discriminations over traditional predictors[33].

Tahil Abmad Munins et al done a study in the year 2010 in 133 ACS patients for assessment of differential leucocyte count in patient with ACS.Univariate analysis of the study revealed higher prevalence of total leucocytes and its sub types ,neutrophils and monocyte in patients of ACS.They concluded that increase in monocyte count is an independent predictor of death and prognostic marker of the extend of myocardial damage in patients with ACS[34].

Syed Shahid Habid et al in 2011 done as observational study in 60 AMI patient,3 serial CRP levels at baseline on admission before 12 hrs of symptoms .Onset ,peak level at 36 -48 hrs and follow up levels after 4 to 6 weeks were analysed and compared between NSTEMI and STEMI.They analysed that STEMI patients have significantly higher peak CRP level compared to NSTEMI patients.These data suggest that inflammatory process play an independent role in pathogenesis of myocardial infarction.Thus they concluded that CRP measurement may assist in risk stratification after myocardial infarction[35] .

Another cross sectional study was Conducted in 404 STEMI patients in madant hospital Tabring –Iran by Samad Ghaffari in 2014.They performed a single CBC analysis to show the value of this inexpensive and widely available test in risk stratification of post STEMI complication over traditional predictors[36].

Ratime eskandarian et al conducted case control study at fatemich hospital ,samrsan gran in 138 MI patients.They compared the leucocyte count in MI patients with LV dysfunction and patients without LV function .From their study they concluded that leucocytosis and neutrophilia in the acute phase of MI are important predictive factor for the development of LV systolic dysfunction. So leucocytosis can be used as risk stratification of such patients[37].

In 2013 Saurar Chattergee et all suggests limited benefit of intensive glycemic control in type 2 diabetics with an MI with significant risk of serious hypoglycemia [38]

Another study done in 2013 by Dubey Rk et al also gave the similar report that serum levels of CRP are higher in patients with NSTEMI.ACS which contribute to the inflammation and thrombosis associated with ACS[39]. This result was more effective by another study conducted in 2003 by Narced Sattar et al .

In 2014 Nis Uriel etc performed a cohort study in 343 patients with acute heart failure .Higher echocardiographic EF was correlated with older age ,increased incidence of hypertension and atrial fibrillation and female gender.They observed that higher EF was correlated with more baseline leucocytosis and higher plasma levels of endothelin-1 and blood urea nitrogen.From their studies they found that patient with acute heart failure,echocardiographic EF is weakly correlated with hemo dynamic measures of left ventricular contractility and outcome,hence it should be interrupted cautionly when evaluating patient admitted due to acute heart failure[40].

Kyle john wilby et al in 2015 performed a retrospective study in all patients admitted with diagnosis of ACS to the CCU at heart hospital in Qatar.Then they determined the predictive factor associated with high glucose level on admission to the CCU.They concluded that diabetics predicts high glucose value on hospital admission for patients with ACS and patients are not being adequately controlled throught CCU stay[41].

Christian stump et al in 2017 correlated the CRP level and risk of developing significant heart failure in patients with acute STEMI[42].This study was supported

by the study conducted by Inder S et al in 2004, they performed a retrospective analysis of the predictive value of baseline CRP for long term outcome in 5010 patients ,with moderate to severe heart failure randomized to valsartan as placebo in the valsarton heart failure trail.CRP level is measured in heart failure patient. Higher level are associated with features of more severe heart failure and are independetely associated with mortality and morbidity[43].

MATERIALS & METHODOLOGY

Study design: This is a prospective study done in the department of medicine ,K.A.P.V ,Trichy medical college hospital .

Period of study:2 years- from 2015 to 2017

Study population: This study is conducted in 100 patients of both sex with typical chest pain ,admitted in the medicine department.

INCLUSION CRITERIA:

Patients admitted with

- Typical chest pain not relieved by rest
- STEMI
- NSTEMI with CPK-MB positive

EXCLUSION CRITERIA:

- known CAD,
- severe renal or liver disease,
- hematologic disorders,
- infectious or inflammatory disease,
- patients on statin therapy were excluded in order to prevent the confounding antiinflammatory effect of statin.

Methodology:

After getting institutional ethical committee approval, Patients were taken for study who was admitted with history of typical chest pain, characterized by apressure,tightness,squeezing,heaviness,or burning and retrosternal location,after radiating to neck,jaw,shoulder or arms,sometimes epigastric regions associated with S4 gallop,mitral regurgitation,murmur,with S3 or rales. Severe ischemia and complication of myocardial infarction are evidenced by electrocardiogram and raised creatin phophokinase-myocardium bound.(Diabetes was defined as use of insulin or oral hypoglycemics if glucose levels > 126 mg/dl. Hyperlipidemia was defined as serum total cholesterol concentration > 200 mg/dl, or serum LDL concentration ≥ 130 mg/dl. The patients with a history of hypertension and who were taking antihypertensive drugs were accepted as having hypertension).Then patients were categorized according to electrocardiogram, creatinine kinase-myocardium bound,and duration of pain.They were classified as

Category I-ST segment elevated myocardial infarction

Category II-non STEMI

Category III-unstable angina

- For category I ,treatment was started in the form of streptokinase injection 1.5 lakh international unit by 1 hour who had elevated ST segment in electrocardiogram.

- Category II & III patients was treated with inj.low molecular weight heparin 5000 IU sixth hourly.
- Asprin,clopidogrel, atorvostatin was given all three category patients.

After treatment was initiated,venous blood samples was collected & the following parameters such as random blood glucose ,cholesterol profile & renal function test were measured using standard techniques.Complete blood haemogram,total and differential leukocyte counts were measured with an automated Advia 2120 hematology analyzer (Roche). Serum CRP and other metabolic profile were measured at hospital arrival.

After patients was stabilized with proper treatment then patients was shifted to ECHO room for evaluating cardiac status from that I utilized ejection fraction to analyze the cardiac performance after myocardial injury in acute coronary syndrome.Then patients was assessed for failure symptoms in the form of pulmonary edema,reduced urine output and raised jugular venous pressure and blood pressure.These parameters were correlated with ejection fraction,differential count ,raised blood sugar,C-reactive protein.

RESULTS

Table no -1: Descriptive statistics

Parameters	Min.	Max.	Mean	S.D
Age(yrs)	27	85	51.50	11.660
SBP(mmHg)	80	170	115.72	17.405
DBP(mmHg)	30	110	77.02	12.768
PR(/mt)	55	130	97.61	17.518

Table no-2: Age distribution

Particular	No. of patients (n=100)	Percentage (100%)
Below 35yrs	9	9.0
36 to 45yrs	27	27.0
46 to 55yrs	30	30.0
56 to 65yrs	23	23.0
66 to 75yrs	8	8.0
76 to 85yrs	3	3.0

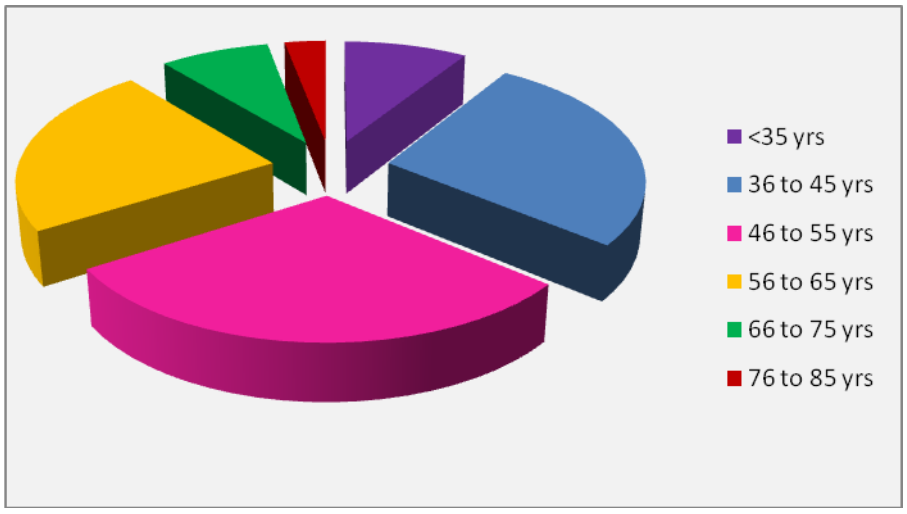


Figure-1: Age distribution

Table no-3: Gender distribution

Particular	No. of patients (n=100)	Percentage (100%)
Male	79	79.0
Female	21	21.0

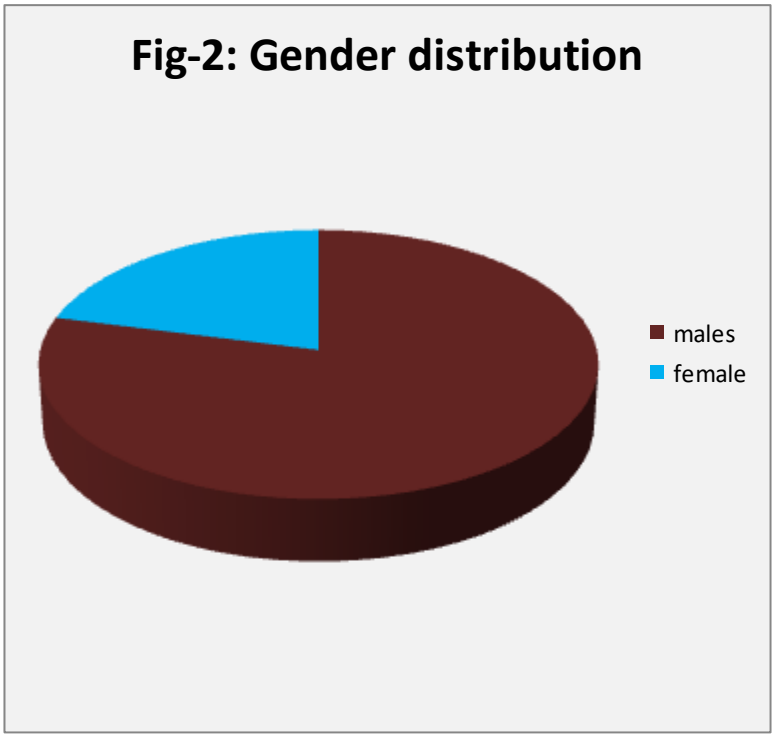


Table no-4: ACS patients with failure symptoms

Parameters	Particular	No. of patients (n=100)	Percentage (100%)
JVP	Absent	40	40.0
	Present	60	60.0
Lung signs	Absent	47	47.0
	Present	53	53.0
Pulmonary edema	Absent	57	57.0
	present	43	43.0
Decreased urine output	Absent	58	58.0
	Present	42	42.0

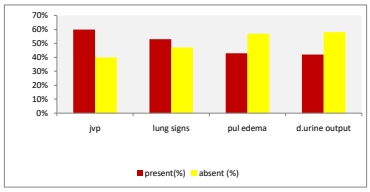


Figure-3: ACS patients with failure symptoms

Table No – 5: Distribution of the respondents and their level of CRP

Particulars	Frequency	Percentage (%)
Normal[<1.2mg/dl]	27	27.0
Elevated [>1.2mg/dl]	73	73.0
Total	100	100.0

Source: Primary data

The above table reveals that vast majority (73 per cent) of the respondents were abnormal level in CRP and remaining 27 per cent were normal level.

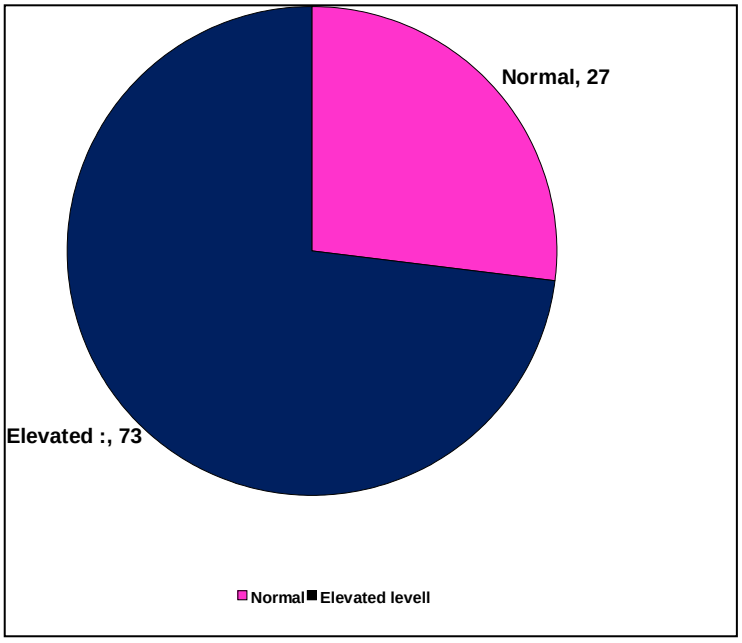


Fig No – 4:Pie Diagram shows that level of CRP

Table No – 6: Distribution of the respondents and their level of EF%

Particulars	Frequency	Percentage
Decreased EF<50%	30	30.0
Normal EF>50%	70	70.0
Total	100	100.0

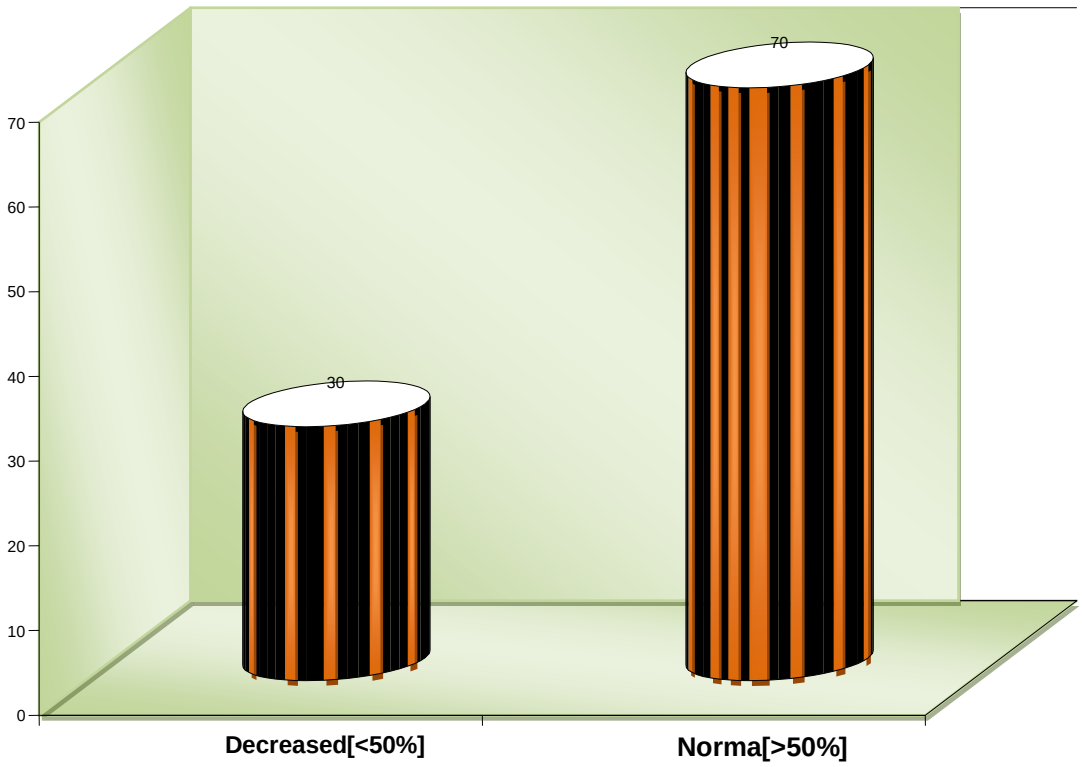


Fig No – 5: Cylinder Diagram shows that level of EF%

Table No – 7: Distribution of the respondents and their level of WBC

Particulars	Frequency	Percentage
Normal	29	29.0
Elevated leve[>11000]	71	71.0
Total	100	100.0

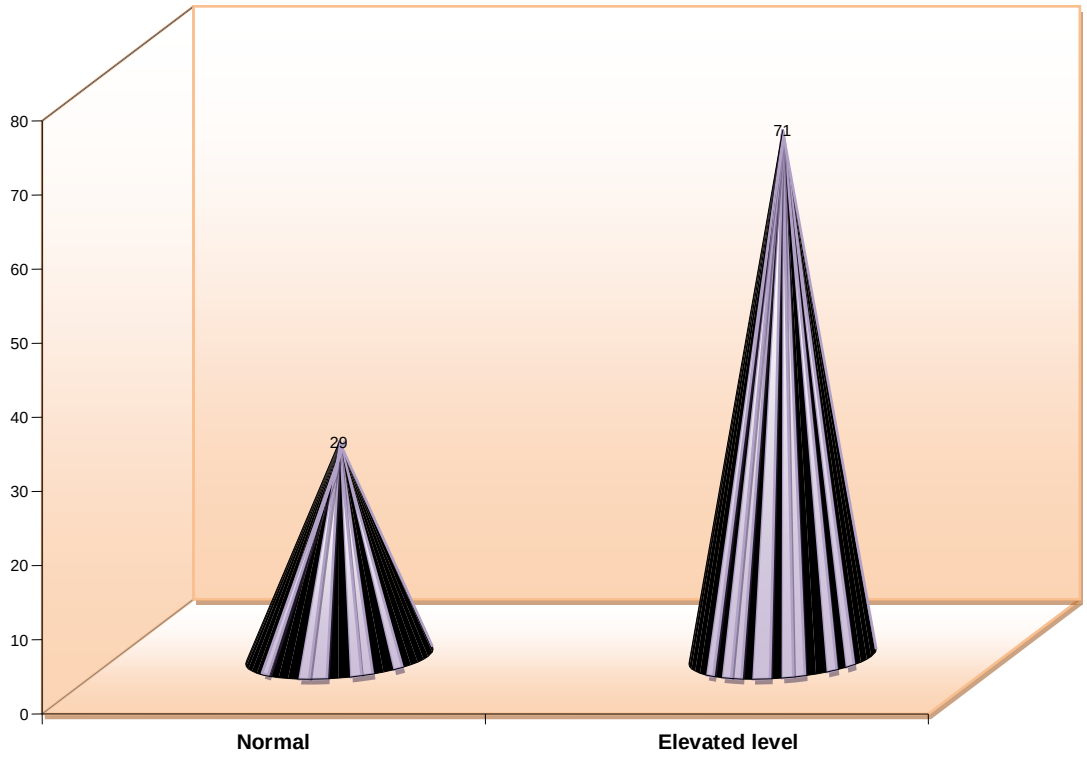


Figure No – 6: Cone diagram shows that level of WBC

Table No – 8 : **Distribution of the respondents and their level of RBS**

Particulars	Frequency	Percentage
Normal	42.0	42.0
Elevated RBS[>140]	58.0	58.0
Total	100	100.0

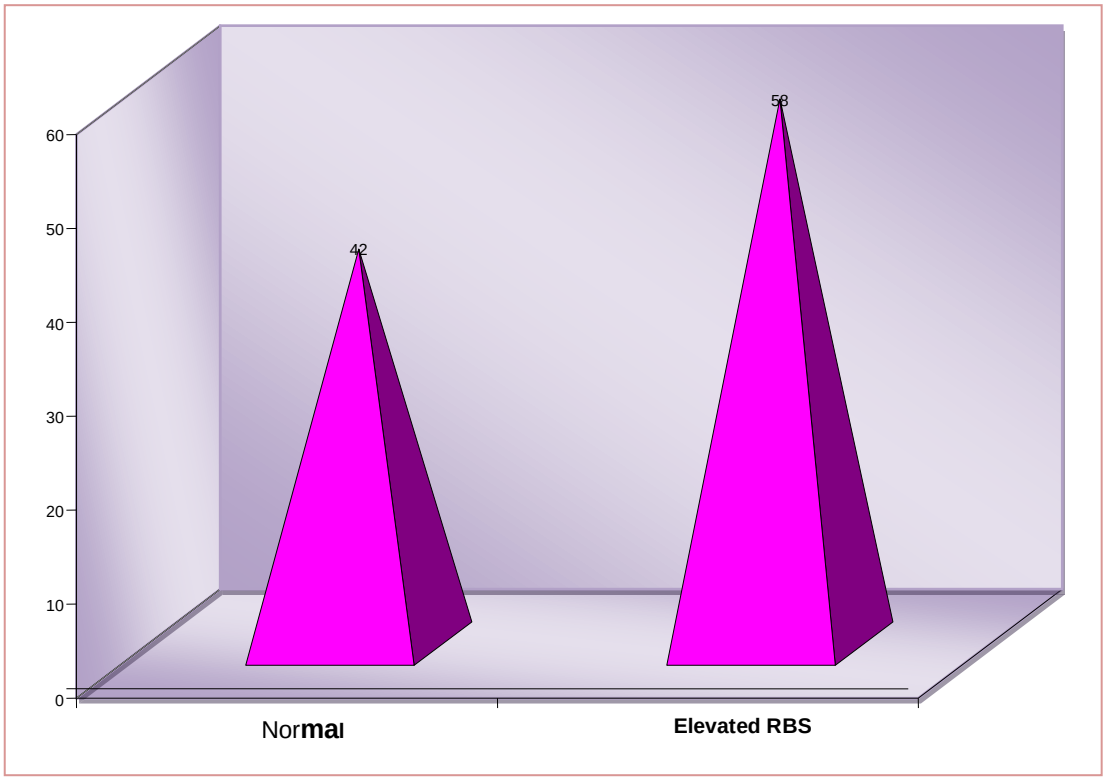


Figure No – 7: **Ven Diagram shows that level of RBS**

Table No -9: Association between CRP and their EF%

CRP	EF%						Statistical inference
	Decreased[<50%]		Normal[>50%]		Total		
	n	*%*	*n*	*%*	*n*	*%*	
Normal	4	13.3%	23	32.9%	27	27.0%	X^2=4.061 Df=1 .044<0.05 Significant
Elevated	26	86.7%	47	67.1%	73	73.0%	
Total no of patients	30	100.0%	70	100.0%	100	100.0%	

Statistical test: Chi-square test was used the above table

N-No of Patients

Research hypothesis (H_1): There is significant association between CRP and their EF%.

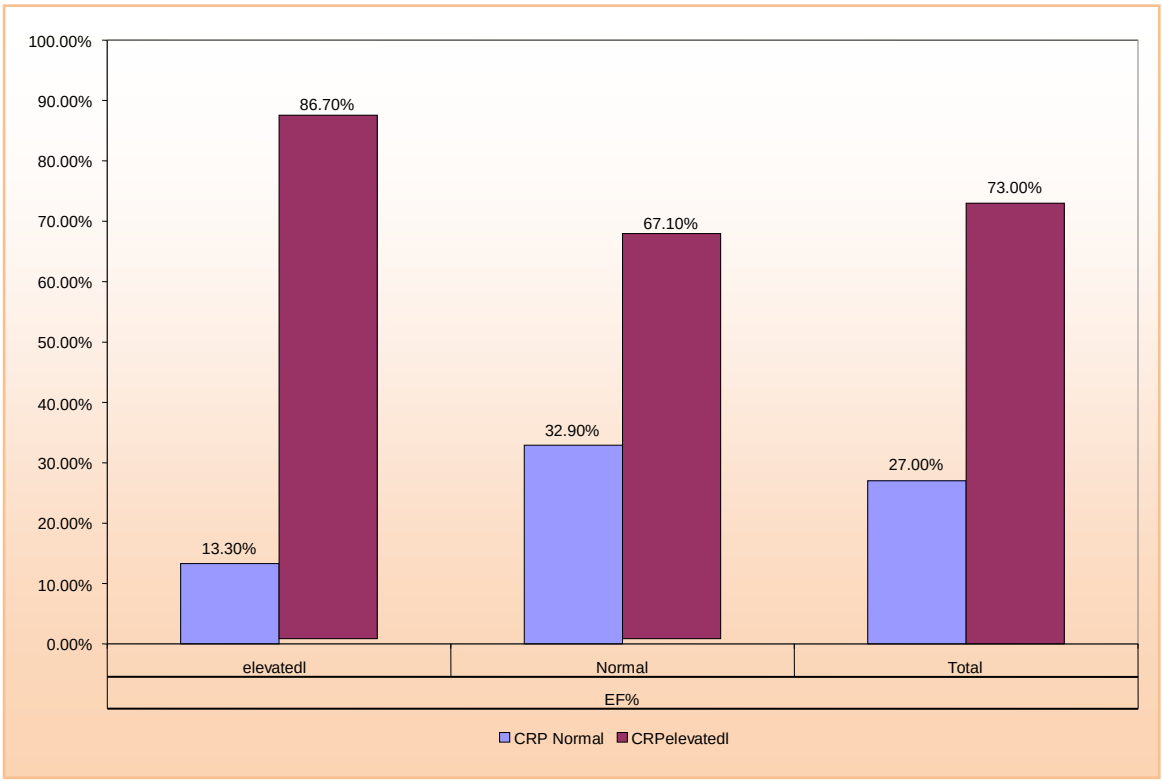


Figure 8: Association between CRP and their EF%

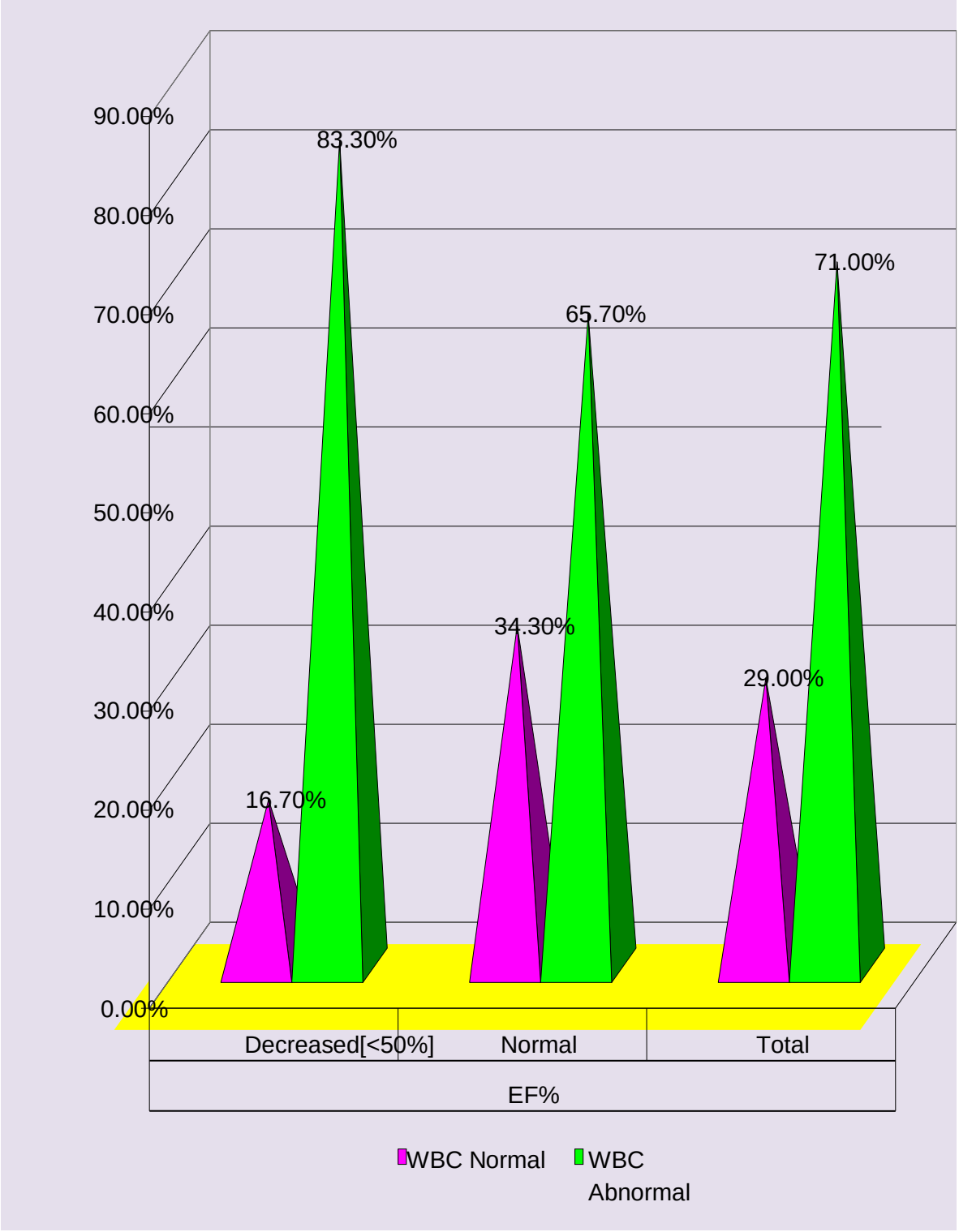
Table No – 10: **Association between WBC and their EF%**

WBC	EF%						Statistical inference
	Decreased[<50%]		Normal[>50%]		Total		
	N	*%*	*N*	*%*	*N*	*%*	
Normal	5	16.7%	24	34.3%	29	29.0%	X^2=4.287 Df=1 .037<0.05 Significant
Elevated >11000	25	83.3%	46	65.7%	71	71.0%	
Total	30	100.0%	70	100.0%	100	100.0%	

Statistical test: Chi-square test was used the above table

N-No of Patients

Research hypothesis (H_1): There is significant association between WBC and their EF%.



Figure– 9: Association between WBC and their EF%

Table No – 11: Association between RBS and their EF%

RBS	EF%						Statistical inference
	Decreased[<50%]		Normal[>50%]		Total		
	N	*%*	*N*	*%*	*N*	*%*	
Normal	5	16.7%	37	52.9%	42	42.0%	X^2=11.291 Df=1 .001<0.05 Significant
Elevated RBS >140	25	83.3%	33	47.1%	58	58.0%	
Total	30	100.0%	70	100.0%	100	100.0%	

statistical test: Chi-square test was used the above table.

N-No of Patients

Research hypothesis (H_1): There is significant association between RBS and their EF%.

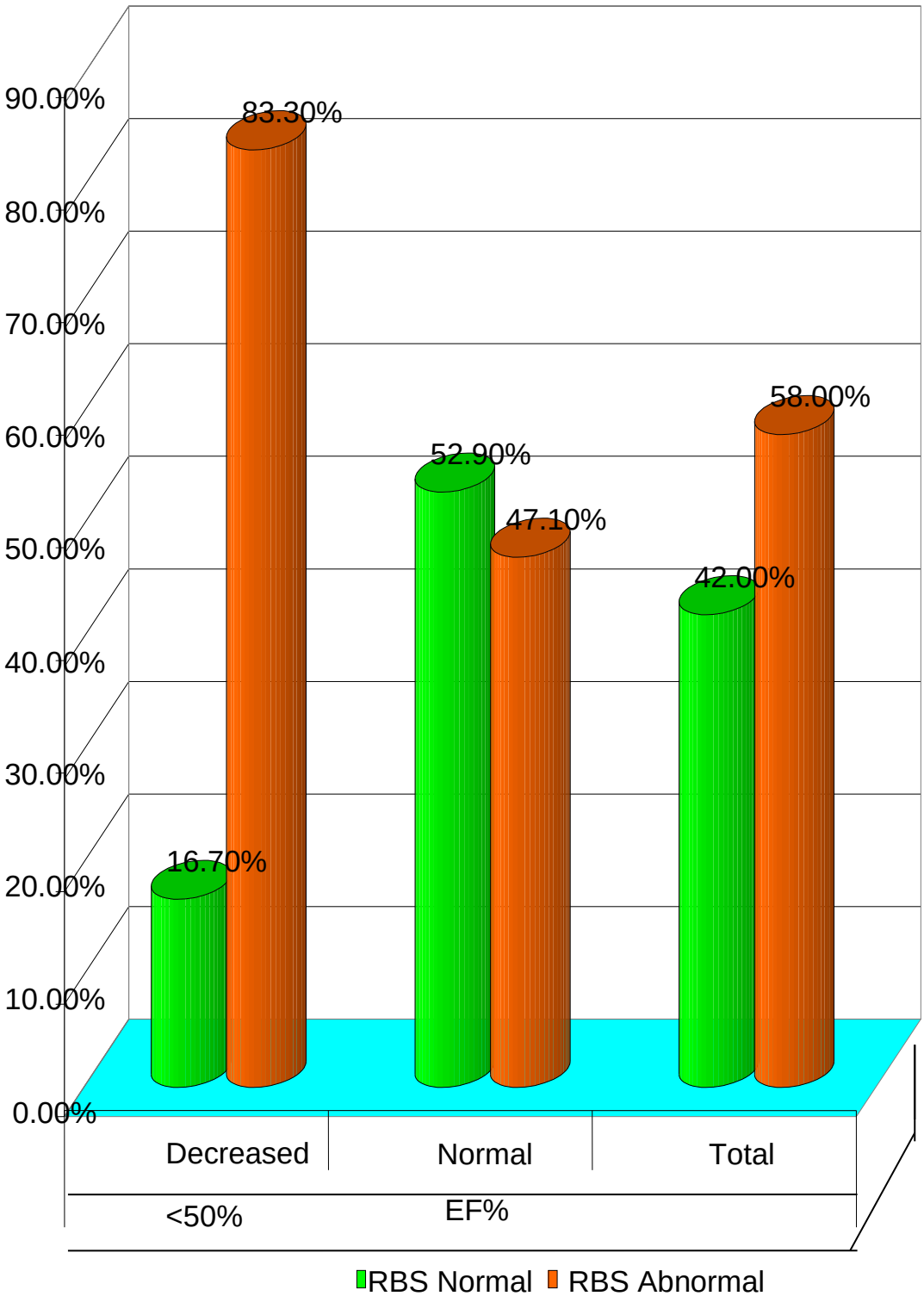


Figure 10 : Association between RBS and their EF%

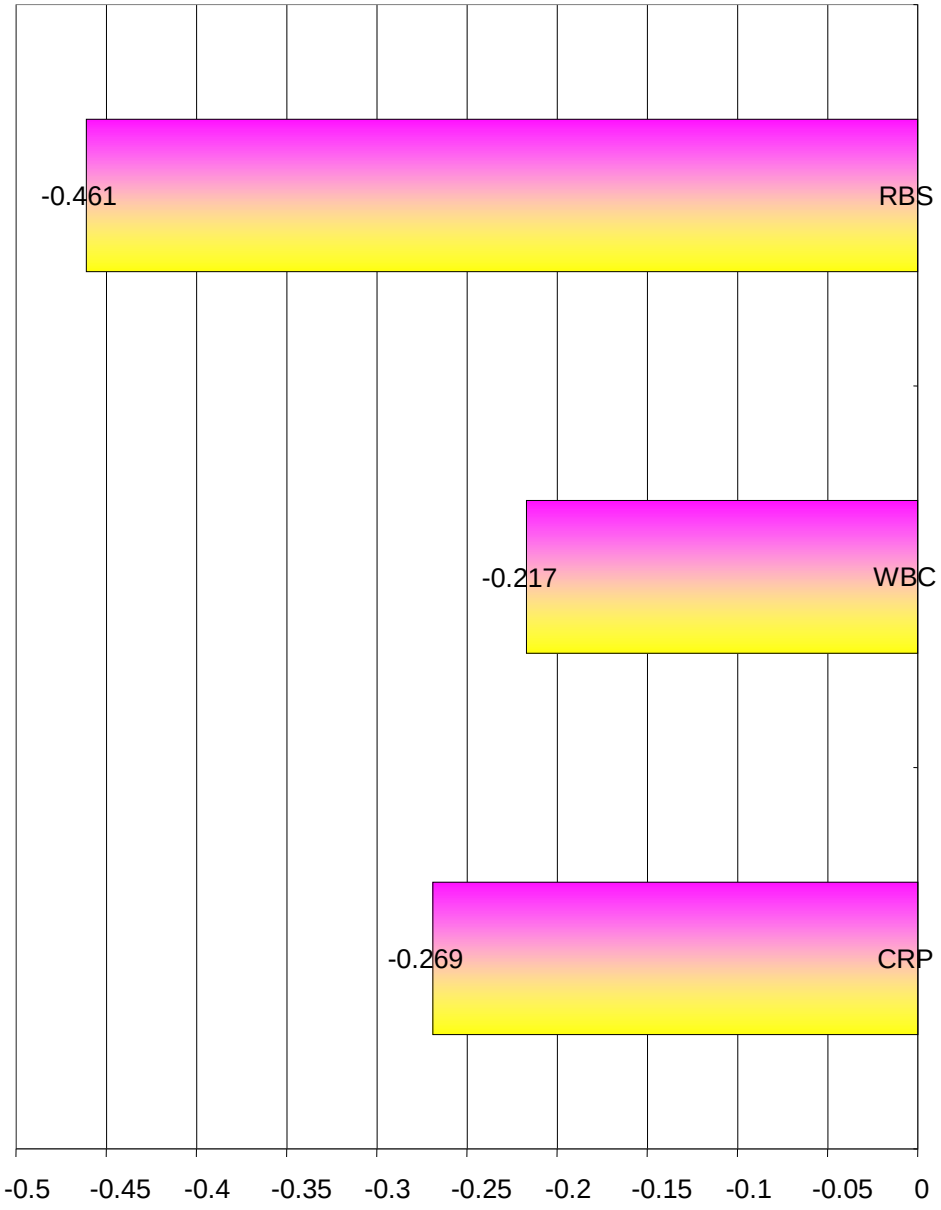
Table No- 12: Karl Pearson Co-efficient Correlation relationship between CRP, WBC, RBS and their EF%

EF%	Correlation value	Level of Significant
CRP	-0.269**	.007<0.01
WBC	-0.217*	.030<0.05
RBS	-0.461**	.000<0.01
*** Correlation is significant at the 0.01 level* ** Correlation is significant at the 0.05 level*		

Statistical test: Karl Pearson Co-efficient Correlation test was used the above table

Research hypothesis (H_1): There is significant relationship between CRP, WBC, RBS and their EF%.

Figure No – 11: Relationship between CRP, WBC, RBS and their EF%



Results:

A total of 100 ACS patients (79 males,21 females) between the age group & yrs was included in the study The mean age was 51.50 ± 11.66 .Mean systolic blood pressure was 115.72 ± 17.40 & diastolic blood pressure 77.02±12.77 .Mean pulse rate was 97.61 ±17.5.

Table -2 shows age distribution in which 9 patients belongs to below 35 yrs,27 patients belongs to 36 to 45 yrs,majority of 30 patients is in the age group of 46 to 55 yrs ,23 belongs to 56 to 65 yrs ,8 were in the age of 66 to 75 yrs and few of about 3 patients belongs to 75 to 85 yrs.Among 100 ACS patients included in the study 79 were males and 21were females(Table-3)

Table no -4 shows that majority of about 60% of ACS patients had raised JVP,53% patients had lung signs,43% patients had symptoms of pulmonary edema,42 % patients had symptoms of decreased urine output

Table no-5 reveals that vast majority 73 % of the ACS patients had elevate level of CRP and remaining 27 % had normal level of CRP,

Table no-6 reveals that vast majority 70 % had normal level of EF% and remaining 30 percent had reduced(less than 50) level,

Table no-7 reveals that vast majority 71% had elevated level of WBC and remaining 29 per cent had normal level,

Table no-8 reveals that more than 58 % had elevated level of RBS and remaining 42 % had normal level of RBS.

Table no-9 reveals that the chi-square test indicates that out of 30 patients, vast majority (86.7 per cent) of the patients had elevated level of CRP when compared to EF%. Therefore, CRP will have more influence over EF%. Hence, the calculated value less than table value (.044<0.05). There is statistically significant association between CRP and their EF%. So, the research hypothesis (H_1) is accepted.

Table no-10 reveals that the chi-square test indicates that out of 30 ACS patients, vast majority (83.3 per cent) of the patients had elevated level of WBC when compared to EF%. Therefore, WBC will have more influence over EF%. Hence, the calculated value less than table value (.037<0.05). There is statistically significant association between WBC and their EF%. So, the research hypothesis (H_1) is accepted.

Table no-11 reveals that the chi-square test indicates that out of 30 patients, vast majority (83.3 per cent) of the patients had elevated RBS level when compared to EF%. Therefore, RBS will have more influence over EF%. Hence, the calculated value less than table value (.001<0.05). There is statistically

significant association between RBS and their EF%. So, the research hypothesis (H_1) is accepted.

Table no-12 reveals that the Karl Pearson Co-efficient Correlation test indicates that there is statistically significant relationship between CRP (-0.269**), WBC (-0.217*), RBS (-0.461**) and their reduced(<50) EF%. Hence, the calculated value less than table value ($p<0.05$). So, the research hypothesis (H_1) is accepted.

Discussion:

In our study,we have quantified the effects of c-reactive protein,white blood cells ,random blood sugars ,ejection fraction in Acute Coronary Syndrome patients.Depending on the patients load in our emergency department we have taken a total of 100 patients which include 79 males & 21 females in the mean age of 51.50 ± 11.66.

Recent studies have found that inflammation plays a important major role in atherosclerosis and Acute Coronary Syndrome. CRP belongs to the pentraxin protein family and is synthesized in hepatocytes and some extrahepatic tissues, such as vascular smooth muscle, atherosclerotic plaques, intracardial tissues.

C-reactive protein is a product of inflammation whose synthesis by the liver is stimulated by cytokines in response to an inflammatory stimulus[39]. In our study we found that the serum level of these C-reactive protein was higher in ACS patient.This result was in consistent with other studies done by Dubey Rk etal (2013),they gave the similar report that serum levels of CRP are higher in patients with ACS[39].

This study was supported by the study conducted by Inder S et al 2004 they performed a retrospective analysis of the predictive value of baseline CRP level which is measured in heart failure patient. Higher level are associated with features of more severe heart failure and are independetely associated with

mortality and morbidity[43].According to him, Interleukin-6 is the primary determinant of the hepatic production of CRP and is produced in monocytes /macrophages,endothelial cells,vascular smooth muscle cells,fibroblast and cardiac myocytes under hypoxic stress[44].left ventricular ,hepatic and renal organ damage induced by low cardiac output, hypoperfusion, hypoxia and venous congestion causes increase in interleukin-6 wich in turn leads to increased CRP production[45].

We also found that there is significant association between CRP and ejection fraction,that is patient with low ejecion fraction showed significant raise in serum CRP when compared to normal ejection faction.Similar result was obtained by the study conducted by Christian stump et al in 2017 correlated the CRP level and risk of developing significant heart failure in patients with acute STEMI[46] . But this was opposed by Kennon S etal in 2003,they conclude that CRP measurement provides only little incremental prognostic information.there is no evidence that CRP is helpful for identifying groups who benefit from particular treatment in ACS.They suggest that only ECG changes and troponin measurement remain the principle tools for risk stratification.and there is no evidence tat CRP measurements provide additional independent information[47].

In patients with ST-elevation MI, rise in hsCRP concentra- tion is related to myocardial damage extent, outcomes and complication risk. According to Chan and Ng, early post infarction related rise in hsCRP is significantly and independently from other prognostic markers related to higher risk of cardiac

(heart rupture, ventricular aneurysm, thrombus formation) and early mechanical complications, but does not prognosti- cate reinfarction . However, new coronary events after MI should be prognosticated only after hsCRP concentration returns to basal level (in 12 weeks), since primary rise in hsCRP concentration reflects acute inflammatory reaction to myo-cardial damage[6]

Shah et al. investigated the prognostic value (discrimina- tion expressed by sensitivity, specificity, AUC, calibration, calibration, reclassification) of hsCRP as the CVD risk factor in these prospective studies: NPHS-II and EAS. Later the systematic review of prospective studies (31 studies, popula-tion of 84,063, 11,252 coronary events), investigating hsCRP and CVD relations, has been done. Multifactorial analysis models prove additional clinical benefit of hsCRP to be minimal[48] A systematic review by Schnell-Inderst et al. has analyzed the prognostic value, effectiveness and costs-benefit ratio of hsCRP together with traditional CVD risk factors and shown that there were not enough data that additional hsCRP testing would improve assessment of CVD risk and patient outcomes. Though a prognostic value of such combined models increases, it remains unclear, whether the increment is clinically relevant. Concerning the costs-benefit ratio, hsCRP evaluation becomes significant when selecting asymptomatic patients with increased hsCRP and normal LDL cholesterol for treatment with statins[49.] Furthermore, a recentanalysis by Chew et al shows that CRP predicts the risk of death or MI at 30 days among patients undergoing

percutaneous coronary intervention. In this setting, the risk associated with elevated CRP was independent of, but additive to, the effect of an increased American College of Cardiology/American Heart Association lesion score[50]. The optimal cutoff point for defining high CRP levels among patients with ACS remains to be determined. The CAPTURE group found that a threshold of 10 mg/l maximized the predictive value of CRP [51]. Several other investigators have used a cutoff point of 3 mg/l for patients with ACS, while the reference ranges for primary prevention populations are lower [52] The precise cause of these different thresholds remains unclear, but it is probably related to heightened vascular inflammation at the time of presentation with ACS.

High levels of CRP in ACS patients have been shown to be a good predictor for death but not AMI recurrence . Many studies have evaluated the association between outcomes and CRP concentrations post-AMI, or peak CRP concentrations on outcome Acute phase levels of CRP at baseline prior to markedelevations of cTnI may prime the body to respond to any necrotic or injured tissue. This theory finds support by De Servi et al who suggest that in ACS populations there is a large variabilityin CRP concentrations, yet those with high CRP at baseline are perhaps more hyper-responsive to stimuli, including circulatingcTnI[53].Acc Ording to kennon etal CRP levels were evaluated in patients with ACS and non-ST elevation on admission and after 12, 24 and 48 h; they shifted from a mean of 4.5 to one of 4.72, 7.79 and 9.99 respectively, with a statistically significant difference between patients taking and not taking aspirin

prior to the onset of symptoms[54].Furthermore, recent studies have suggested that CRP may play a direct role in promoting inflammatory atherosclerosis. CRP is not only a marker of systemic vascular inflammation but also plays an important key role in plaque disruption and subsequent thrombosis[55].

According to SK Thomas etal (2003),In ACS, the levels of troponin and CRP provide important, different, and complementary prognostic information. With increasing levels of any of the markers, there is a commensurate rise in mortality. At any detectable troponin, there is also a raised risk of a later MI. The combination of both markers allows the best prediction of mortality. The use of the combination of these markers will provide an important tool for the selection of patients for clinical trials and also for identification of patients for different treatment alternatives[56].

Another study demonstrated that a total WBC count inexcess of 10 000 per _l was associated with a risk that was approximately twice that seen when the WBC count wasat or below 4000 per _l. This excess risk was independent of gender, smoking history, blood pressure, and cholesterol level[57]

According to Hoffman etal in 2004 they suggests tat Inflammation has been demonstrated to be an important risk factor for the development of cardiovascular events. Patientswith elevated WBC counts have been shown to have a higher risk of developing an AMI and to be at higherrisk for adverse events during the acute setting. In this reviewwe reviewed the clinical data on the association betweenWBC count of AMI patients (on admission) and thprognostic

outcome of these patients, we discussed possible and the possible correlation between high WBC count and the development of reperfusion injury, the no-flow phenomenon and congestive heart failure.It is possible that measuring WBC count, WBC sub-populations, cell adhesion molecule and cytokine levelsshould be used in order to help us to have a new and maybean improved way for risk stratification of patients admitted with AMI[58].

Atherosclerotic plaque is characterized by infiltrates of monocytes /macrophages and lymphocytes which have transmigrated from the vascular space into the subendothelial layers of large and medium sized arteries[59].In human ,myocardial necrosis begins in the subendocardium at 30-40 minutes after the onset of coronary occlusion.Reperfusion injury occurs due to increased fibrinolytic leading to restoration of coronary blood flow[60].A large infract enhance cytokines synthesized & secreted by the monocytes & macropages to induce the migration into the infracted region[61].Next is early appearance of neutrophil in the infract zone with heavy infiltration by 1-3 days ,followed by infract healing and replacement fibrosis[62].In our study, data showed that there is a strong association between leucocytosis and ejection fraction,which was made more effective by the previous study done by Tahil abmad munins et al in 2010, their study revealed that higher prevalence of total leucocytes and its sub types (i.e) neutrophils and monocyte in patients of ACS. several experimental and clinical studies have provided compelling evidence that WBCs are important mediators of cardiac injury through release of proinflammatory cytokines. Imbalance in cytokine

release has been demonstrated in patients with acute coronary syndromes in which a significant increase of interferon gamma and tumour necrosis factor-alpha production is observed accompanied by a significant decrease of interleukin- 10 production[62].Myeloperoxidase (MPO) levels may be elevated among individuals with CAD. Myeloperoxidase is an enzyme secreted by a variety of inflammatory cells, including activated neutrophils, monocytes, and certain tissue macrophages, such as those found in atherosclerotic plaque. The enzyme is not released until leukocyte activation and degranulation.

Myeloperoxidase may convert LDL into a high-uptake form for macrophages, leading to foam cell formation, and may also deplete nitric oxide, contributing to endothelial dysfunction. In a recent case-control study,increasing levels of leukocyte-MPO and blood-MPO were significant predictors of the risk for CAD, such that after adjustment for white blood cell count and Framingham risk score, individuals in the highest quartile of blood-MPO had a 20-fold higher risk of CAD than individuals in the lowest quartile[8]. According to MADJID etal(2004) suggestes that a high leukocyte count is associated with increased CHDrelated morbidity and mortality in various patient populations and clinical settings. It also appears to be an independent risk factor, regardless of atherosclerotic disease status. Thus, it may turn out to be a less expensive and more readily The increased risk of coronary thrombosis associated with leukocytosis, together with the association of UA with activation of circulating leukocytes, and the well-established risk of leukocyte plugging on reperfusion

raise the question of the safety of stem cell therapies that rely on intracoronary infusion of leukocytes or systemic injections of granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor, which raise leukocyte counts.These approaches may increase the risk of thrombosis and may be more problematic than the small arrhythmogenic potential of subendocardial injections[63].

According to Murtagh and Anderson etal(2004) , the higher level of myoperoxidase secreted by the activation and degranulation of leucocytes is an important prognostic factor in cardiac patient[32].This was in consistent with our study.

As leucocyte assessment are cheap and routinely performed ,some study suggested that it can be used for risk stratification.A study conducted by Antman Braunwald as well as Green et al suggested that leucocyte is a sensitive test for diagnosis of MI ,as it is associated with impaired perfusion in the epicardium and myocardium.This was supported by Hansen's study ,they found that an elevated WBC count was accompanied by decreased epicardial & myocardial perfusion,thromboresistance and a higher rate of cardiac failure and death. According to Mueller et al hypercoagulability ,endothelial dysfunction, necrosis of pro inflammatory myocytes and a no-reflow phenonmenon are all associated with leucocytosis,this is mainly due to reperfusion of the ischemic tissue causes neutrophils and platelet to form plaque in the microvasculaturewich causes loss of

vascular reserve and enlargement of infract area leading to ventricular function and ventricular arrthymias.their findings showed that in the acute phase of MI ,leucocytosis and neutrophilia are important predictor of heart failure-i.e patient with leucocytosis were 3.6 times more likely to develop heart failure,while those with neutrophilia had 4.29 times higher risk of developing heart failure[29].

Our study result was in consistent with Samad Ghaffari study,they performed a single CBC analysis for the risk stratification in post STEMI complication patients. Similar result was obtained by Ratime Eskandarian *et al,* they concluded that leucocytosis and neutrophilia in the acute phase of MI are important predictive factor for the development of LV systolic dysfunction.So leucocytosis can be used as risk stratification of ACS patients[64]**.**

Acute hyperglycemia on admission for acute coronary syndrome worsens the prognosis in patients with and without known diabetes. Postulated mechanisms of this observation include prothrombotic effects. The aim of this study was to evaluate the effect of elevated glucose levels on blood clotting in acute coronary syndrome patients.

We also got a strong association between hyperglycemia & ejection fraction, as the hyperglycemia increases, EF decrease, Our result was similar to the study conducted by Christophare *et al.*

According to Jitender Mokta *et al.*, in 2017,Unrecognized diabetes and stress hyperglycemia at admission to coronary care unit in ACS patients increase the risk of cardiovascular events and intervention improves the outcome.This suggests that improved glucometabolic care reverse the negative effect of hyperglycemia on cardiovascular complications.

CONCLUSION

- Acute Coronary Syndrome patients with increased random blood sugars had reduced Ejection fraction when compared to non hyperglycemic patient.So hyperglycemic status in ACS patient is an independent predictor of cardiovascular mortality & morbidity.
- serum level of inflammatory marker CRP is elevated in Acute coronary syndrome patients with reduced Ejection fraction.
- There is leucocytosis in ACS patient with reduced myocardial ejection fraction

So above said three parameter are positively correlated with decreased ejection fraction .If these parameter is elevated in ACS patients that means, the ejection fraction was less than 50%.So quantification of these three parameters (1).CRP,(2).WBC Count, (3) Random Blood Sugar in acute coronary syndrome will predict the morbidity and mortality and helps roughly, to estimate the ejection fraction without echo cardiogram**.**

LIMITATION OF THE STUDY:

1. The sample size was small.
2. All complication of acute coronary syndrome patients was not included.
3. Correlation between the heart failure signs with these parameters was not done and justified.
4. Comparison of these parameters before & after treatment of ACS patient was done.

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PROFORMA

SERIAL NO : IP. NO: DOA:

DOD:

- NAME:
- AGE:
- SEX:
- OCCUPATION:
- MARITAL STATUS:
- ADDRESS:
- TELEPHONE NO:
- STATUS AT DISCHARGE:

[1]. PRESENTING COMPLAINTS:

[2]. HISTORY OF PRESENTING ILLNESS:

H/o Chest Pain:

- Site: Precordial/ Retrosternal
- Epigastric/ Shoulder/ Neck
- Time of onset:
- Nature: Squeezing, Crushing, Compressive, Tightness
- Radiation: Arm/ Back/ Epigastric/ Neck

- Frequency:
- Severity Aggravating Factor:
- Relieving Factor:
- Associated sweating:

H/O Breathlessness:

- Onset: Sudden/ Gradual Grade: I/II/III/IV
- H/O Orthopnea: Yes/ No Wheeze: Present/ Absent
- H/O PND: Yes/No
- Associated symptoms

H/O Palpitation :

- Onset: Acute/ Insidious Duration
- Nature: intermittent/ continuous
- Aggravating Factors: Exertion/ Excitement
- Relieving Factors

H/O Swelling Of Legs/ Face:

- Onset: Acute/ Insidious Duration:
- Associated with pain: yes/ No Diurnal Variation: Yes /No

G.Nausea /Vomiting :

H.Excessive Sweating:

[3]. PAST HISTORY

- Hypertension,diabetesmellitus,similar h/o previous episodes

[4]. PERSONAL HISTORY

- Diet Vegetarian Mixed
- Smoking Duration
- Alcohol Duration
- Tobacco Chewing Duration Quantity

[5]. GENERAL PHYSICAL EXAMINATION

- Built :Well/Moderate/ Poor
- Nourishment :Obese/Average /Poor
- Pallor :Present/ Absent
- Cyanosis: Present/ Absent
- Icterus: Present/ Absent
- Clubbing :Present/ Absent
- Pedal edema :Present/ Absent
- Lymphadenopathy :Present/ Absent
- Extremities :Warm/ Cold

[6].VITAL SIGNS

- Pulse rate:

- Blood pressure:
- Respiratory rate:

[7]. **SYSTEMIC EXAMINATION** :

CVS EXAMINATION :

- Pulse –rate,rhythm,volume,character,condition of vessel wall,radio femora delay
- JVP –Normal /Raised

Inspection :

- Precordium :Normal/Bulged
- Apical impulse :Visible / Non Visible
- Other pulsation:

Palpation :

- Apical impulse- Location, Character :
- Palpable Heart Sounds :
- Thrills Apex :
- Parasternal area :

Auscultation

- Heart sounds :

- S3/S4 :Present/ Absent
- Murmur: Timing/Location/Character/Radiation/Grade
- Pericardial rub:
- Basal crepitations :

Others

- KILLIP CLASS:

RESPIRATORY SYSTEM:

PER ABDOMEN:

CENTRAL NERVOUS SYSTEM

[8].INVESTIGATIONS :

Blood :

- Haemoglobin
- Total count
- Differential count
- ESR
- CRP

Urine:

- Albumin, Sugar

- Microscopy

Biochemistry

- Plasma glucose
- On admission
- Lipid profile

Electrocardiography (ECG)

CONCLUSIONS

- Thrombolysis - Done/Not Done

In Hospital Complications

- CCF/LVF
- Cardiogenic Shock
- Arrythmias
- Thromboembolism
- Pericarditis
- Rupture Of Interventricular Septum
- Rupture Of Papillary Muscle
- Aneurysm
- Any Other
- Follow Up Upto Date Of Discharge

K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE
TIRUCHIRAPALLI -1
INSTITUTIONAL ETHICS COMMITTEE

CERTIFICATE OF CLEARANCE

This is to certify that the project work titled Quantification of CRP, Differential count, Blood Sugar in ACS proposed by Dr.P.Lenin, part of fulfillment of M.D/M.S course in the subject of General Medicine for the year 2015-2018 by The Tamilnadu Dr.MGR Medical University has been cleared by the Ethics committee.

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ABBREVIATIONS

ACS	-	Acute Coronanary Syndrome
AGE	-	Advanced glycation end product
BP	-	Blood Pressure
CHD	-	Coronary Heart Disease
CK	-	Creatine Kinase
CK-MB	-	Creatine Kinase-mb
CPK-MB	-	Creatine Phosphor Kinase-myocardium bound
CRP-C	-	Reactive Protein
CVD	-	Cardiovascular Diseases
DBP	-	Diastolic Blood Pressure
DBP	-	Diastolic Blood Pressure
DC	-	Differential Count
EF	-	Ejection Fraction
ESC	-	European Society of Cardiology
ESH	-	European Society of Hypertension
ESR	-	Erythrocyte sedimentation rate
H_2O_2	-	Hydrogen Peroxide
HbA_{1c}	-	Glycated Hemoglobin
HDL-C	-	High Density Lipoprotein Cholesterol
HS –CRP	-	High Sensitive
ICAM	-	Intra cellular adhesion molecule
ISH	-	International Society of Hypertension
LDL-C	-	Low Density Lipoprotein Cholesterol
MIR	-	Microsomal RNA
Non STEMI	-	St Elevated Myocardial Infarction
PCAM	-	Platelet cell adhesion molecule
PR	-	Pulse Rate

RBS	-	Random Blood Sugar
SBP	-	Systolic Blood Pressure
SMC	-	Smooth muscle cell
STEMI	-	Stelevated Myocardial Infarction
TC	-	Total Count
VCAM	-	Vascular cell cellular adhesion molecule
VLDL-C	-	Very Low Density Lipoprotein Cholesterol
WBC	-	Whole Blood Count